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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 401/12, 277/04, 205/04, 207/04, 279/00, 221/06, 285/16, 231/04, A61K 31/44, 31/445, 31/54, 31/40

A1

(11) International Publication Number: **WO 96/31504**

(43) International Publication Date: 10 October 1996 (10.10.96)

(21) International Application Number: PCT/US96/04460

(22) International Filing Date: 1 April 1996 (01.04.96)

(30) Priority Data:
08/416,244 4 April 1995 (04.04.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/416,244 (CIP)
Filed on 4 April 1995 (04.04.95)

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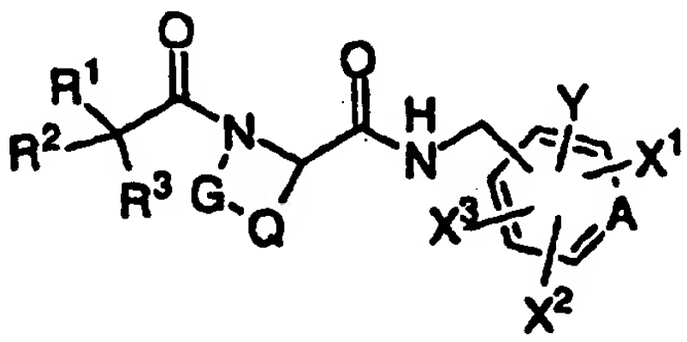
(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

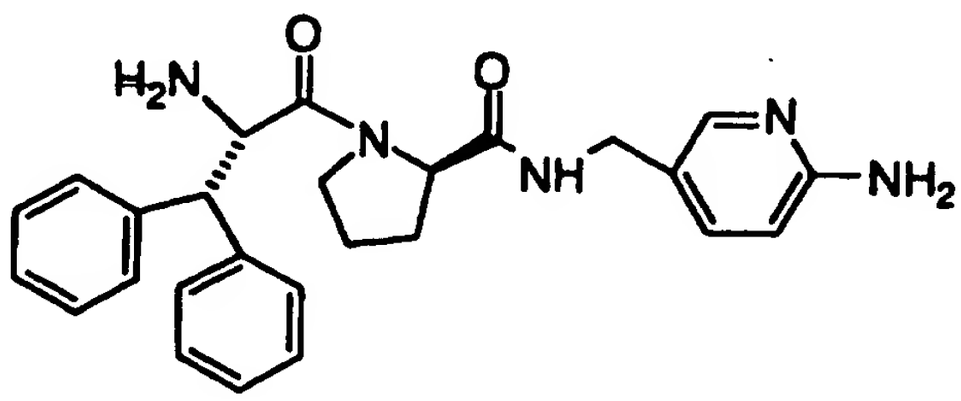
(54) Title: THROMBIN INHIBITORS

(57) Abstract

A compound which inhibits human thrombin and has the structure (I) such as (II).



(I)



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TITLE OF THE INVENTION
THROMBIN INHIBITORS

BACKGROUND OF THE INVENTION

Thrombin is a serine protease present in blood plasma in the form of a precursor, prothrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the solution plasma protein, fibrinogen, into insoluble fibrin.

Edwards *et al., J. Amer. Chem. Soc.*, (1992) vol. *114*, pp. 1854-63. describes peptidyl a-ketobenzoxazoles which are reversible inhibitors of the serine proteases human leukocyte elastase and porcine pancreatic elastase.

European Publication 363 284 describes analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the substrate peptide has been replaced by hydrogen or a substituted carbonyl moiety.

Australian Publication 86245677 also describes peptidase inhibitors having an activated electrophilic ketone moiety such as fluoromethylene ketone or α-keto carboxyl derivatives.

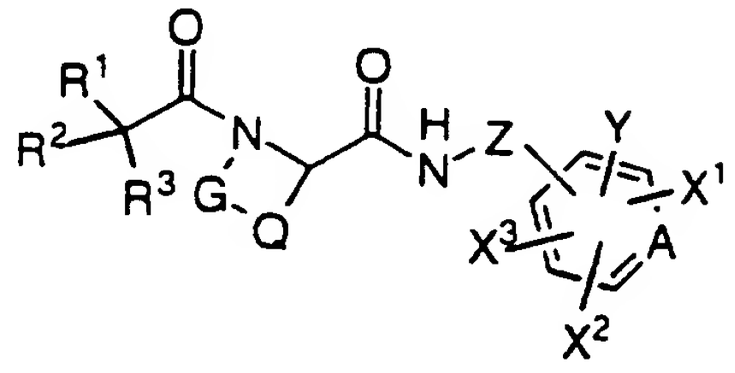
Thrombin inhibitors described in prior publications contain sidechains of arginine and lysine. These structures show low selectivity for thrombin over other trypsin-like enzymes. Some of them show toxicity of hypotension and liver toxicity.

European Publication 601 459 describes sulfonamido heterocyclic thrombin inhibitors, such as N-[4-[(aminoimino-methyl)amino]butyl]-1-[N-(2-naphthalenylsulfonyl)-L-phenylalanyl]-L-prolinamide.

WO 94/29336 describes compounds which are useful as thrombin inhibitors.

SUMMARY OF THE INVENTION

Compounds of the invention have the following structure:



wherein

A is C or N;

X^1, X^2 and X^3, each independently attached to a ring carbon atom, are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

Y, attached to a ring carbon atom, is H, NH_2 or OH;

Z is $-(CH_2)_{1-3}-$;

R^1, R^2, and $R^{2'}$ are independently

hydrogen,

phenyl,

mono- or di-halogenated phenyl,

naphthyl,

biphenyl,

a 5- to 10-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,

C_{1-4} alkyl,

branched C_{1-4} alkyl,

C_{3-7} cycloalkyl,

C_{5-12} bicyclic alkyl,

C_{11-16} tricyclic alkyl,

$R^4(CH_2)_n$,

$(R^4)_2(CH)$.

$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S,

where n is 1, 2, 3 or 4;

R^3 is

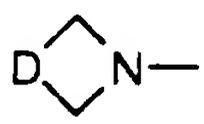
hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 10-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
$-COR^5$,
$-OR^6$,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{1-4} alkoxy,

C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

R^5 is

-OH,
$-OR^6$,
$-N(R^7)_2$, where R7 is same or different, and



where D is $-CH_2CH_2-$, $-CH_2-O-CH_2-$, or $-CH_2-NH-CH_2-$;

R^6 is C_{1-4} alkyl;

R^7 is hydrogen or C_{1-4} alkyl;

G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

These compounds show selectivity for thrombin inhibition over inhibition of trypsin and other trypsin-like enzymes. Trypsin-like enzymes (such as trypsin, thrombin, factor xa, kallikrein, plasmin, urokinase, and plasminogen activator) are serine dependent enzymes that catalyze hydrolysis at arginyl and lysyl peptide bonds.

The invention includes a composition for inhibiting loss of blood platelets, inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents,

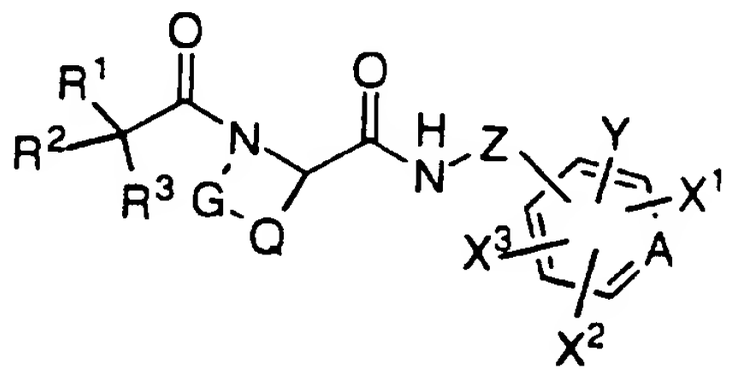
and thrombolytic agents. The compositions can be added to blood, blood products, or mammalian organs in order to effect the desired inhibitions.

The invention also includes a composition for preventing or treating unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels, in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents.

The invention also includes a method for reducing the thrombogenicity of a surface in a mammal by attaching to the surface, either covalently or noncovalently, a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the invention have the following structure:



wherein

A is C or N;

X^1, X^2 and X^3, each independently attached to a ring carbon atom, are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

Y, attached to a ring carbon atom, is H, NH_2 or OH;

Z is $-(CH_2)_{1-3}-$;

R^1, R^2, and $R^{2'}$ are independently

hydrogen,

phenyl,

mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 10-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2(CH)$,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is

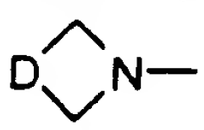
hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently

phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 10-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
$-COR^5$,
$-OR^6$,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{1-4} alkoxy,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

R^5 is

-OH,
$-OR^6$,
$-N(R^7)_2$, where R7 is same or different, and



where D is $-CH_2CH_2-$, $-CH_2-O-CH_2-$, or $-CH_2-NH-CH_2-$;

R^6 is C_{1-4} alkyl;

R^7 is hydrogen or C_{1-4} alkyl;

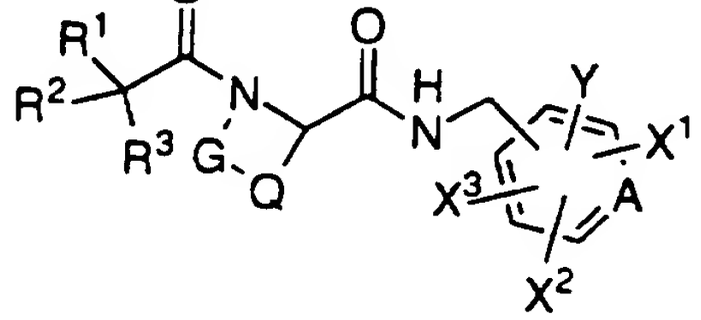
G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or

$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

In one class, compounds of the invention have the following structure:



wherein

A is C or N;

X^1, X^2 and X^3, each independently attached to a ring carbon atom, are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

Y, attached to a ring carbon atom, is hydrogen, NH_2 or OH;

R^1, R^2, and $R^{2'}$ are independently

hydrogen,

phenyl,

mono- or di-halogenated phenyl,

naphthyl,

biphenyl,

a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,

C_{1-4} alkyl,

branched C_{1-4} alkyl,

C_{3-7} cycloalkyl,

C_{5-12} bicyclic alkyl,

C_{11-16} tricyclic alkyl,

$R^4(CH_2)_n$,

$(R^4)_2(CH)$,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is
hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or

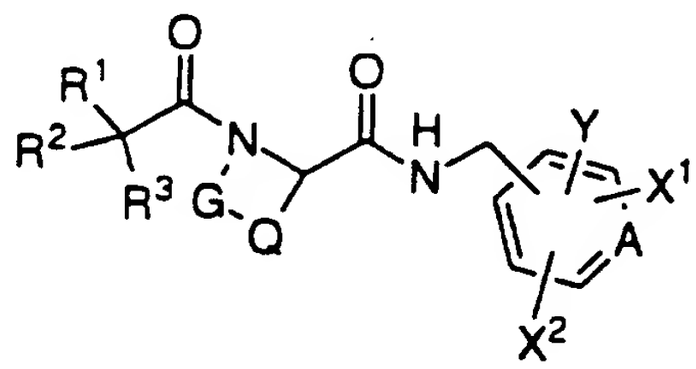
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

In a subclass of this class, the compounds have the following structure:



wherein

A is C or N;

X^1 and X^2, each independently attached to a ring carbon atom, are independently selected from the group consisting of H and C_{1-4} alkyl;

Y, attached to a ring carbon atom, is hydrogen, NH_2 or OH;

R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting

of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2(CH)$,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is

hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently

phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and

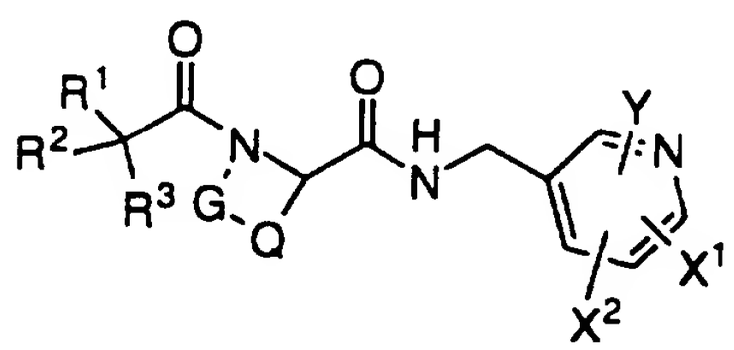
from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

In a group of this subclass, compounds of the invention have the following structure:



wherein

X^1 and X^2, each independently attached to a ring carbon atom, are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;
Y, attached to a ring carbon atom, is hydrogen or NH_2;
R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,

mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicylic alkyl,
C_{11-16} tricylic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2CH$, wherein R^4 is the same or different,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is

hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently

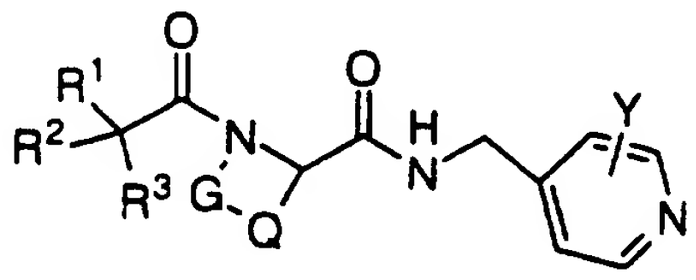
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated. and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N. O and S.
COOH.
C_{1-4} alkyl.
branched C_{1-4} alkyl.
C_{3-7} cycloalkyl.
C_{5-12} bicyclic alkyl. or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2. or
NR^1CH_2: and

Q is SCH_2. or
$(CH_2)_r$ where r is 1 or 2.

and pharmaceutically acceptable salts thereof.

In another group of this subclass. compounds of the invention have the following structure:



wherein

Y. attached to a ring carbon atom. is H or NH_2;

R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2CH$, wherein R^4 is the same or different,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S;

where n is 1, 2, 3 or 4;

R^3 is
hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or

different;

R^4 is independently

phenyl,

mono- or di-halogenated phenyl,

naphthyl,

biphenyl,

a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,

COOH,

C_{1-4} alkyl,

branched C_{1-4} alkyl,

C_{3-7} cycloalkyl,

C_{5-12} bicyclic alkyl, or

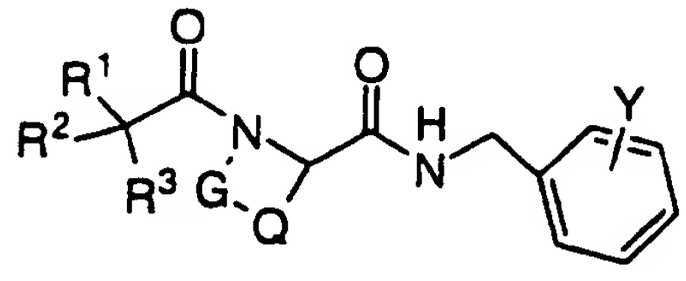
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2, or NR^1CH_2; and

Q is SCH_2, or $(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

In another group of this subclass, compounds of the invention have the following structure:



wherein

Y, attached to a ring carbon atom, is hydrogen or NH_2;

R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2CH$, wherein R^4 is the same or different,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is
hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,

$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2, or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

Some abbreviations that may appear in this application are as follows.

ABBREVIATIONS

Designation	
BOC (Boc)	t-butyloxycarbonyl
HBT(HOBT or HOBt)	1-hydroxybenzotriazole hydrate
BBC reagent	benzotriazolyloxy-bis(pyrrolidino)-carbonium hexafluorophosphate
PyCIU	1,1,3,3-bis(tetramethylene)-chlorouronium hexafluorophosphate
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
$(BOC)_2O$	di-t-butyl dicarbonate
DMF	dimethylformamide
Et_3N or TEA	triethylamine
EtOAc	ethyl acetate
TFA	trifluoroacetic acid
DMAP	dimethylaminopyridine
DME	dimethoxyethane
BH3-THF	Borane-tetrahydrofuran complex
D-Phe(3,4-Cl_2)	D-3,4-Dichlorophenylalanine
D-3,3-dicha	D-3,3-Dicyclohexylalanine
Pro	Proline
Arg	Arginine
Gly	Glycine
D-3,3-diphe	D-3,3-Diphenylalanine

The compounds of the present invention may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. A racemate or racemic mixture does not imply a 50:50 mixture of stereoisomers.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also,

combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "Halo", as used herein, means fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, single negatively-charged species, such as chloride, bromide, hydroxide, acetate, trifluroacetate, perchlorate, nitrate, benzoate, maleate, tartrate, hemitartrate, benzene sulfonate, and the like.

Cyclic alkyl, bicyclic alkyl, and tricyclic alkyl refer to saturated ring systems, including spiro systems, fused systems, and bridged systems, unsubstituted or substituted with oxygen to form carbonyl carbon systems, or C_{1-2} alkyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl,

benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

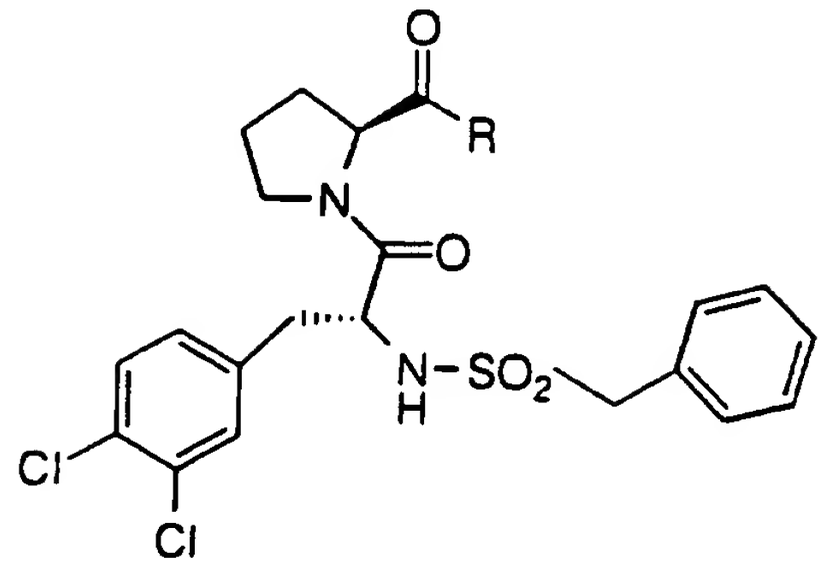
The pharmaceutically-acceptable salts of the compounds of Formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

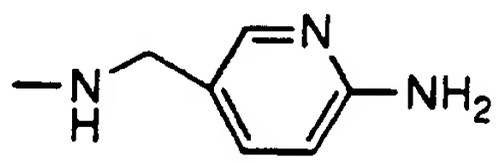
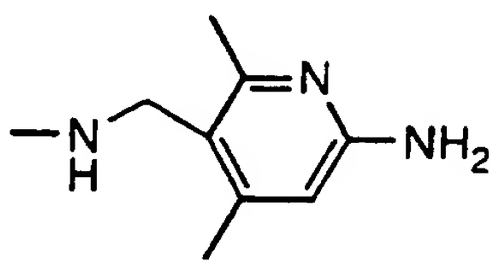
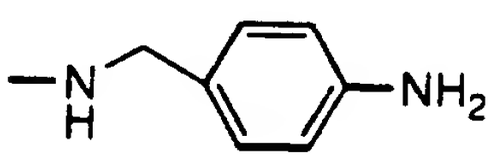
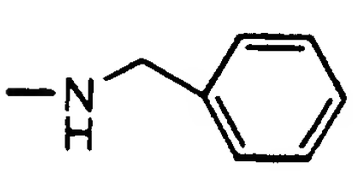
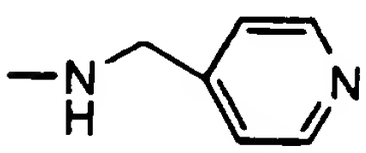
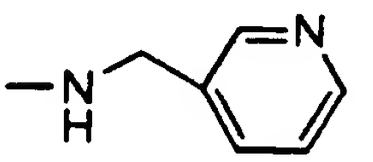
Amide couplings used to form the compounds of this invention are typically performed by the carbodiimide method with reagents such as dicyclohexylcarbodiimide, or l-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide. Other methods of forming the amide or peptide bond include, but are not limited to the synthetic routes via an acid chloride, azide, mixed anhydride or activated ester. Typically,

solution phase amide coupling are performed, but solid-phase synthesis by classical Merrifield techniques may be employed instead. The addition and removal of one or more protecting groups is also typical practice.

The compounds shown in the tables below are exemplary compounds of the present invention. having Ki (uM) for human thrombin IIa in the range between 0.00005 and 100:

TABLE 1



R	Scheme
	1
	2
	
	
	
	

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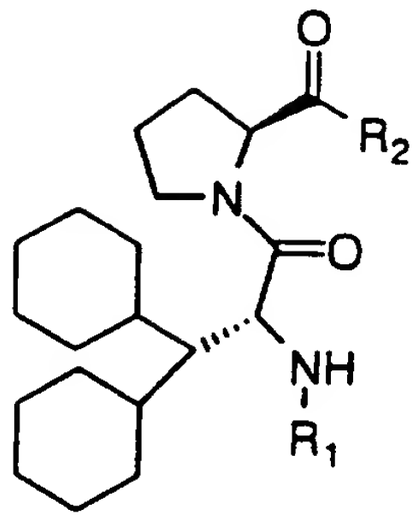


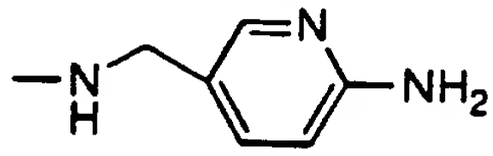
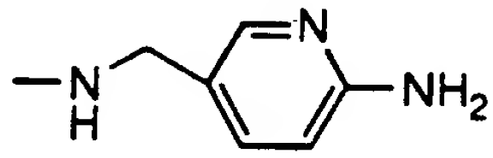
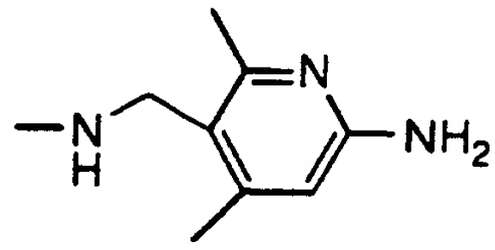
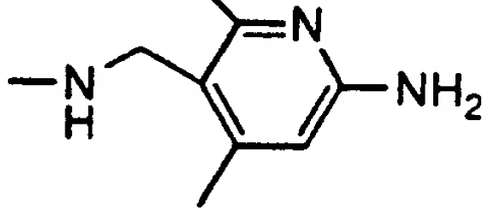
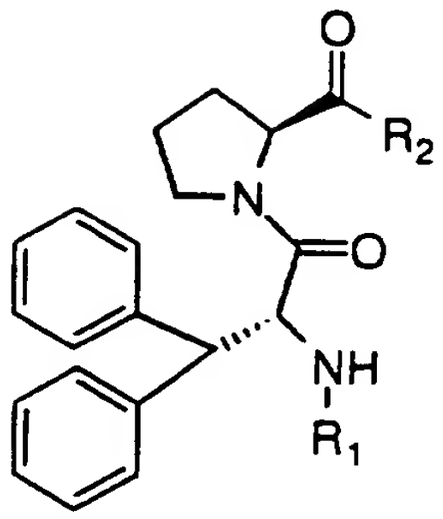
R_1	R_2	Scheme
BOC		1
H		1
BOC		2
H		2

TABLE 3



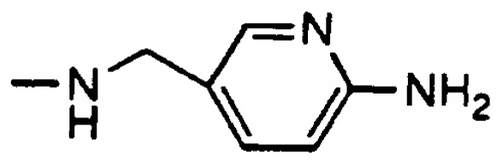
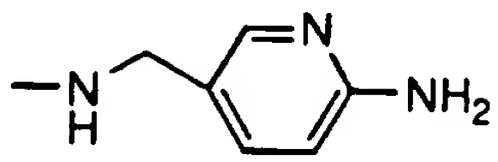
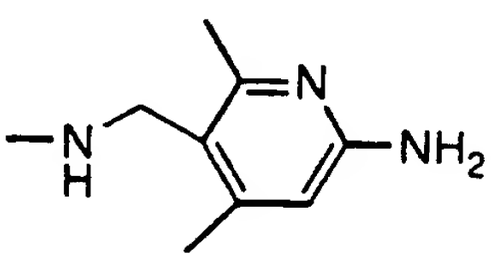
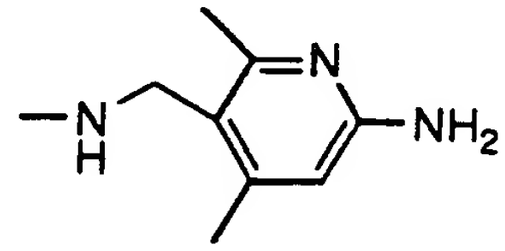
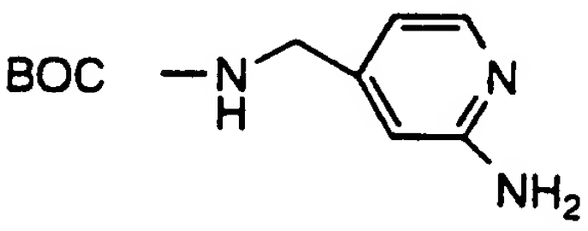
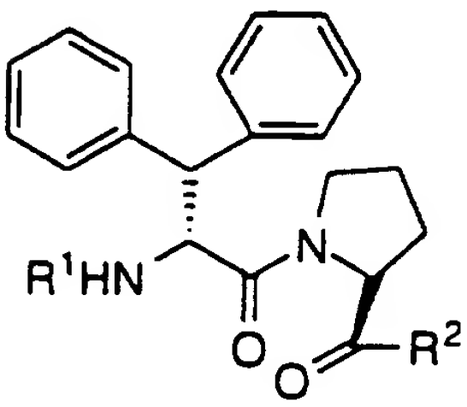
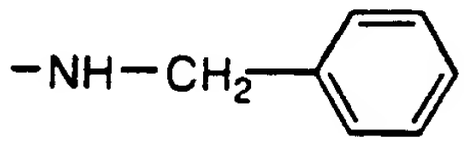
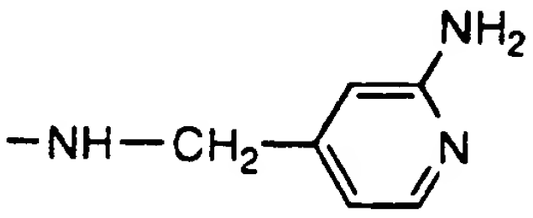
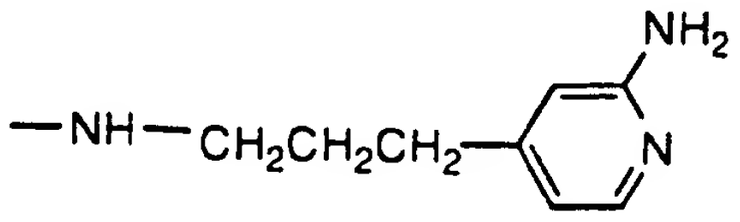
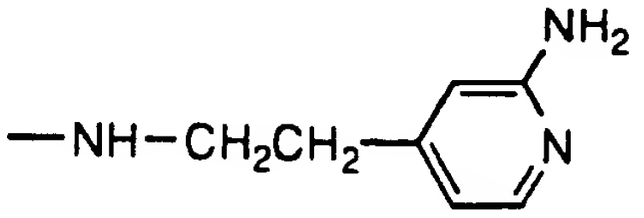
R_1	R_2	Scheme
BOC		1
H		1
BOC		2
H		2
BOC		2

TABLE 3 (CONT'D)



R^1	R^2
H	
H	
H	
H	

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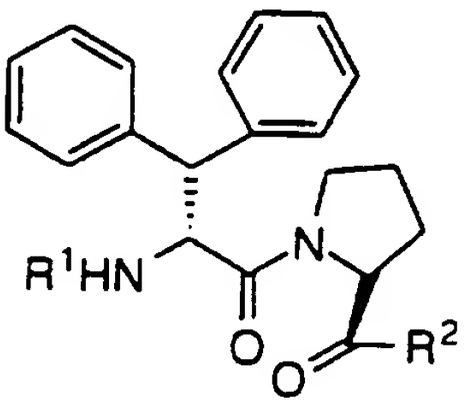


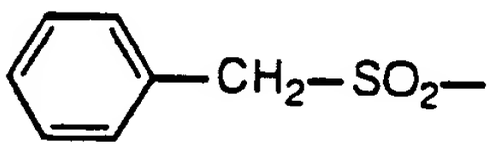
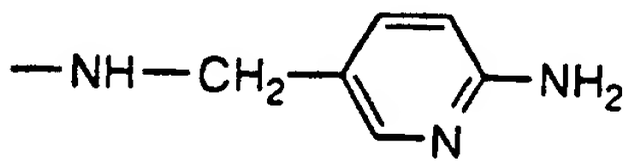
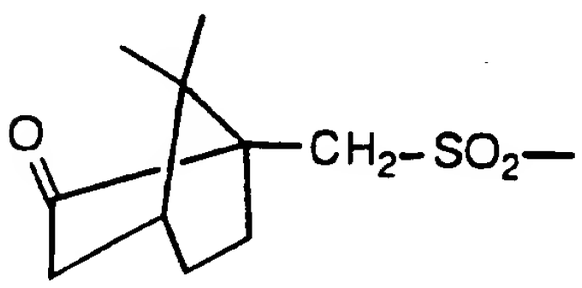
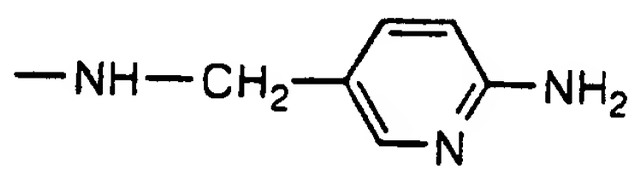
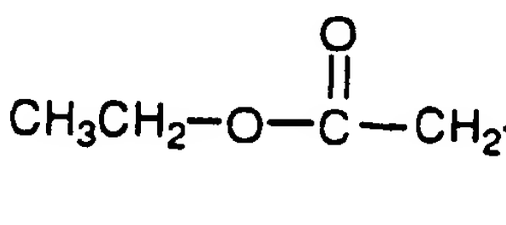
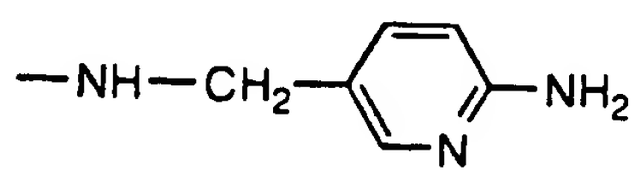
R^1	R^2
	
	
	

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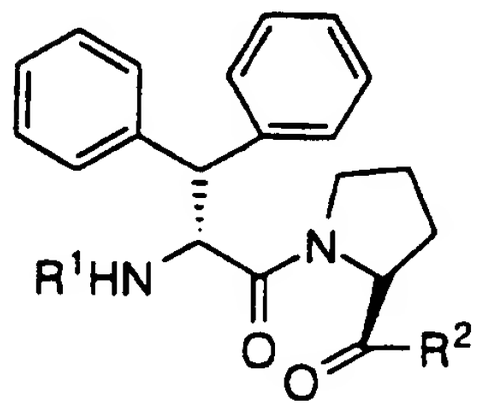
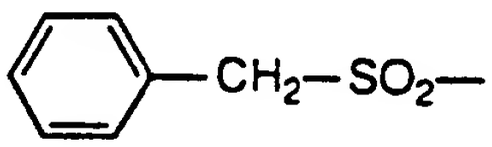
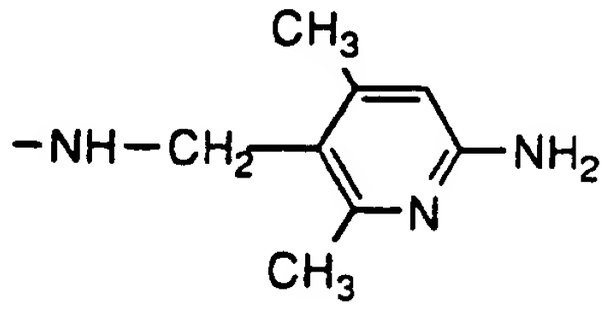
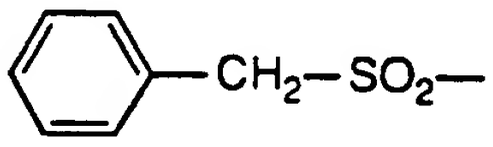
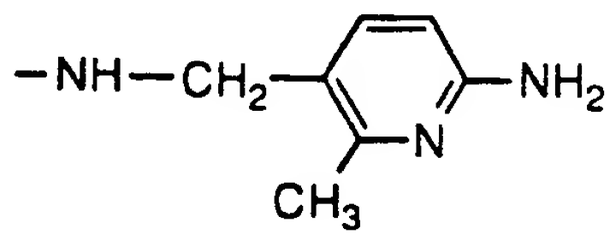
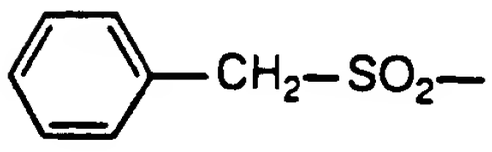
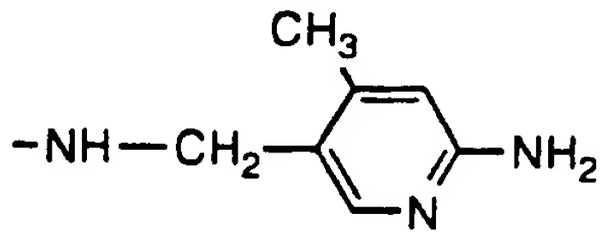
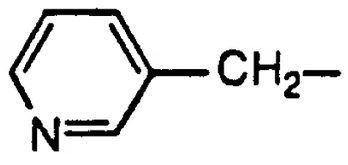
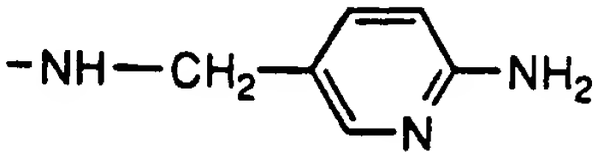
TABLE 3 (CONT'D)



R^1	R^2
	
	
	
	

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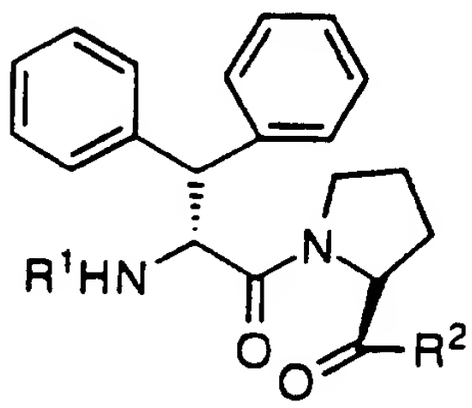


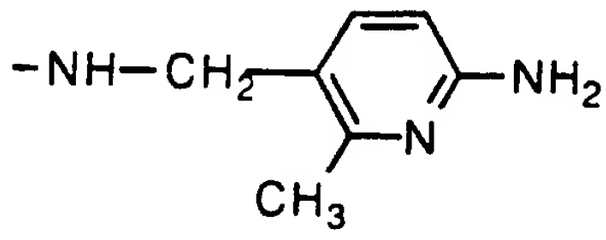
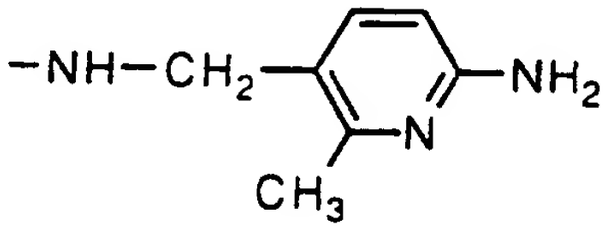
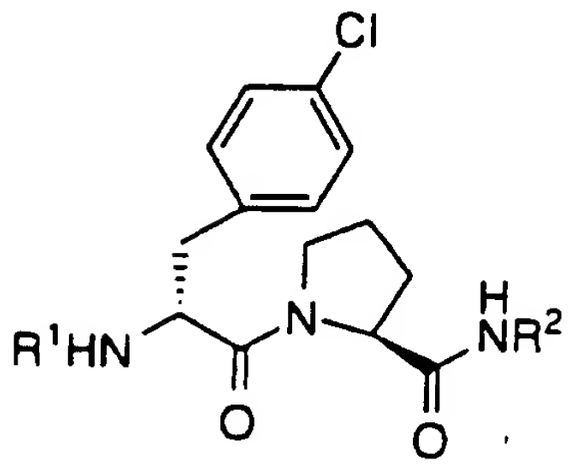
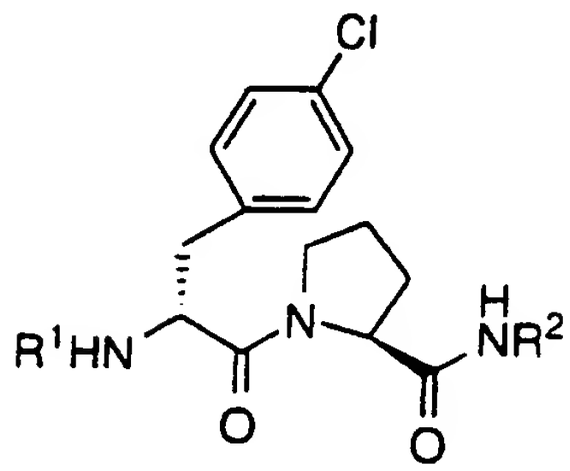
R^1	R^2
BOC	
H	

TABLE 4



R^1	R^2
$(CH_3)_3C-O-C(=O)-$	$-CH_2$-(2-amino-4-pyridyl)
$(CH_3)_3C-O-C(=O)-$	$-CH_2$-(2-amino-3-pyridyl)
H	$-CH_2-C_6H_4-NH_2$
H	$-CH_2$-(2-amino-4-pyridyl)

TABLE 4 (CONT'D)



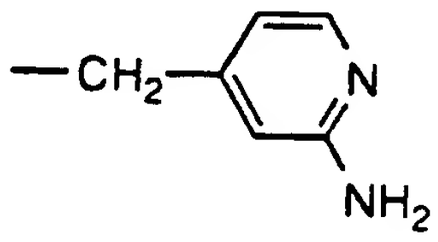
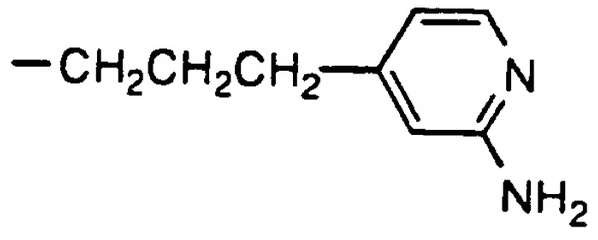
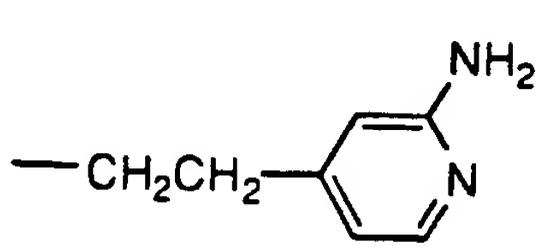
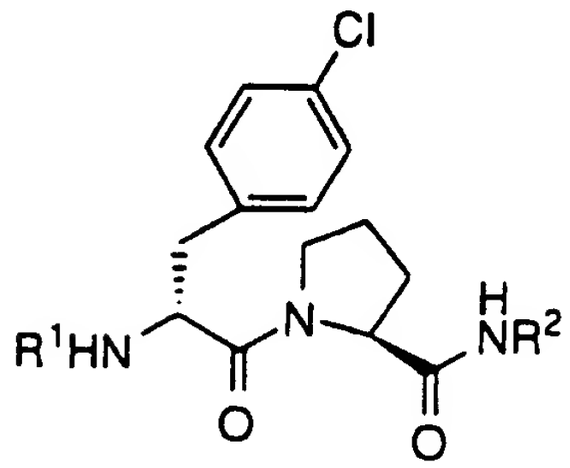
R^1	R^2
H	
H	
H	

TABLE 4 (CONT'D)



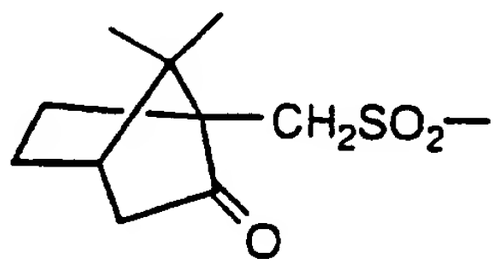
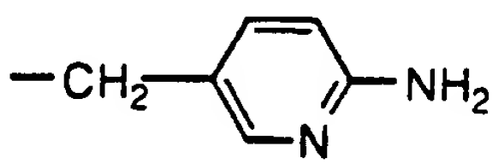
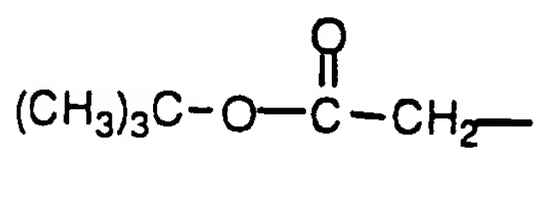
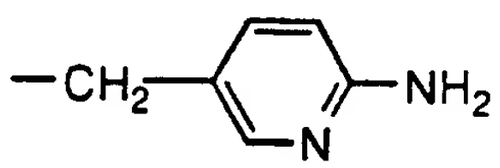
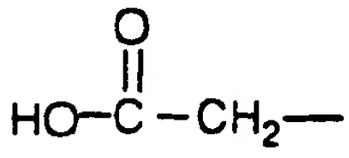
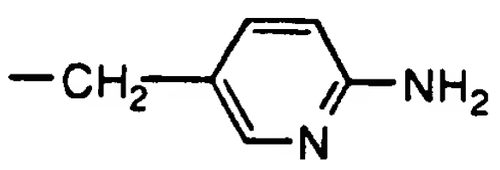
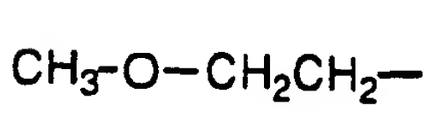
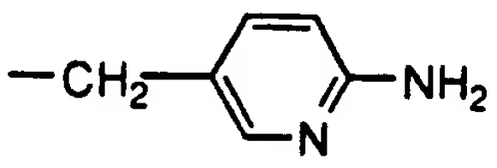
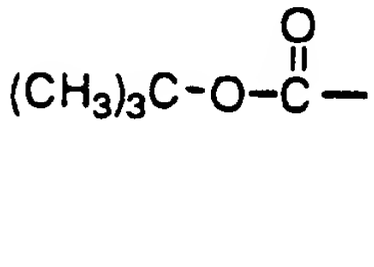
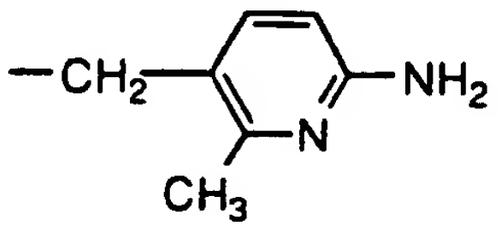
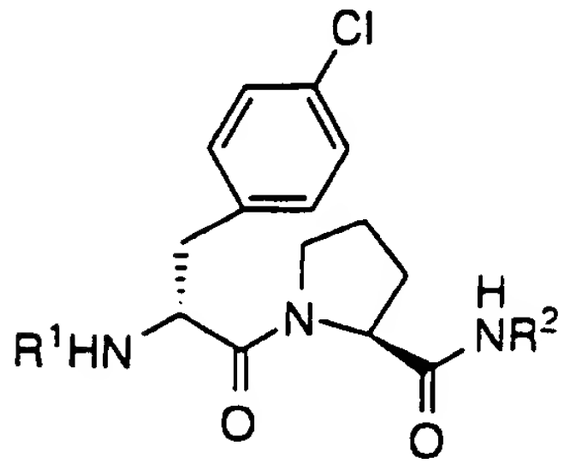
R^1	R^2
	
	
	
	
	

TABLE 4 (CONT'D)



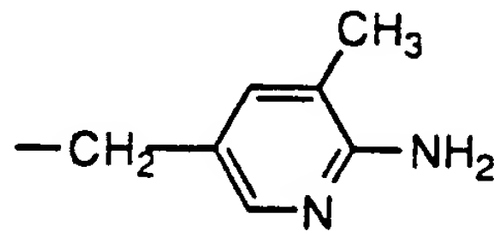
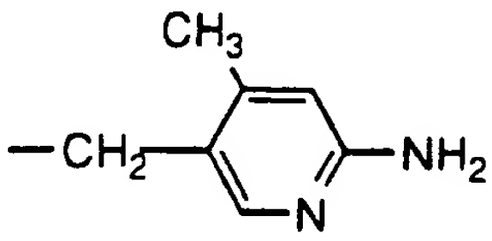
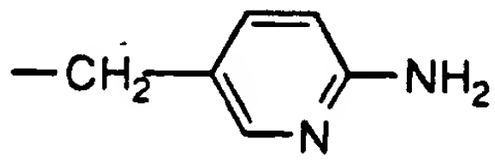
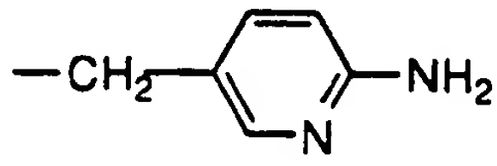
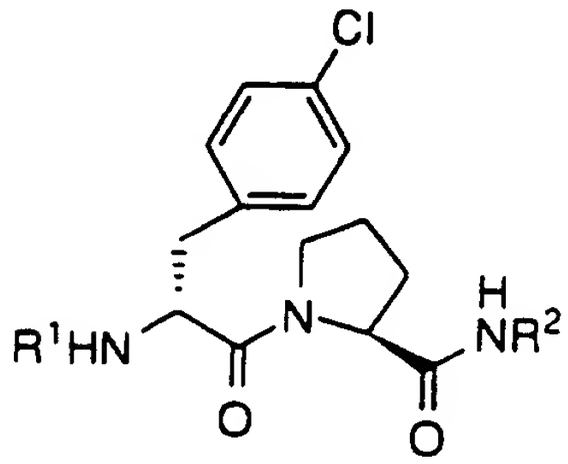
R^1	R^2
$(CH_3)_3C-O-C(=O)-$	
$(CH_3)_3C-O-C(=O)-$	
$(CH_3)_3C-NH-C(=O)-CH_2-$	
$(CH_3CH_2)_2N-C(=O)-CH_2-$	

TABLE 4 (CONT'D)



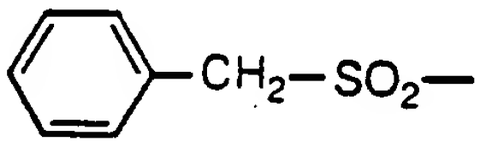
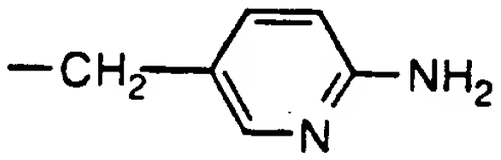
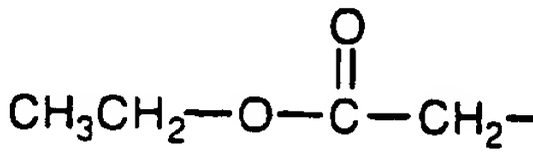
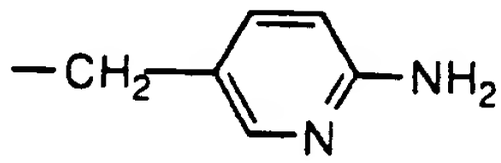
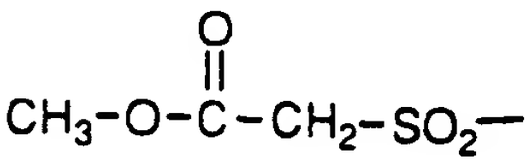
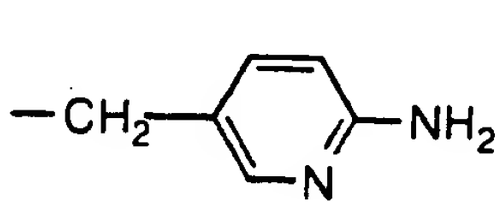
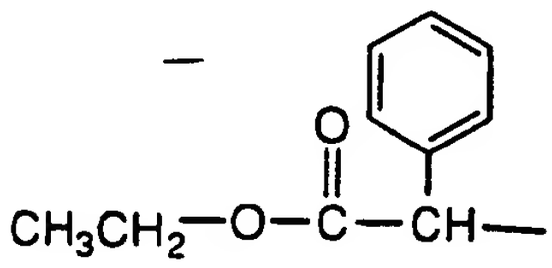
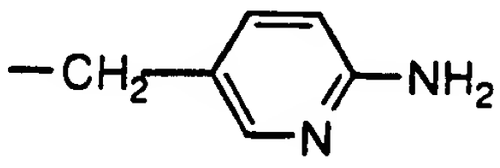
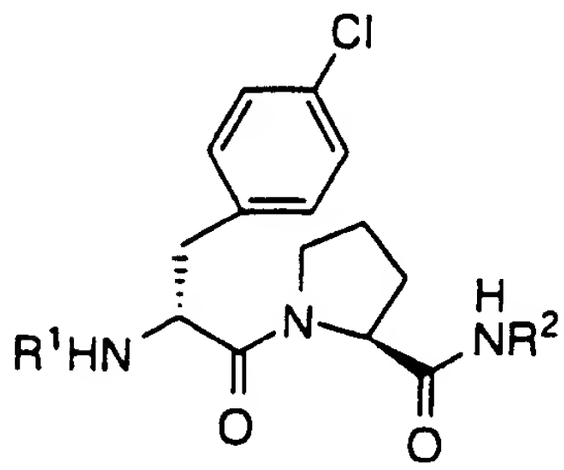
R^1	R^2
	
	
	
	

TABLE 4 (CONT'D)



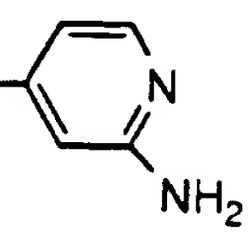
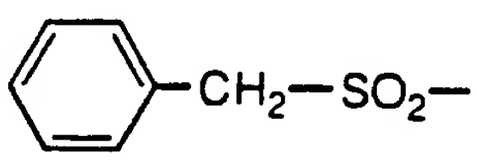
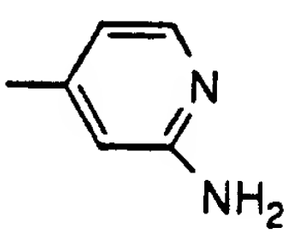
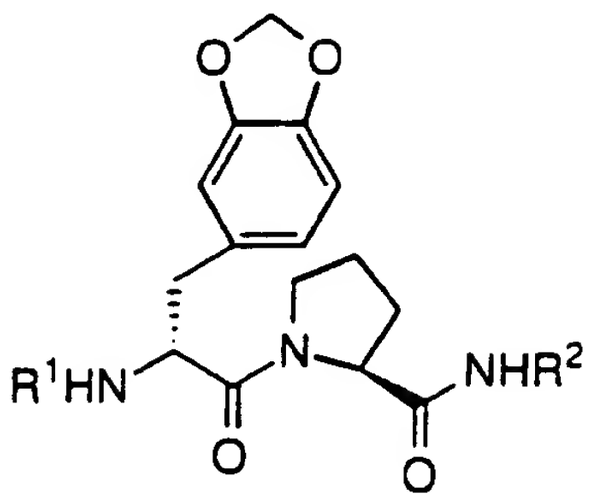
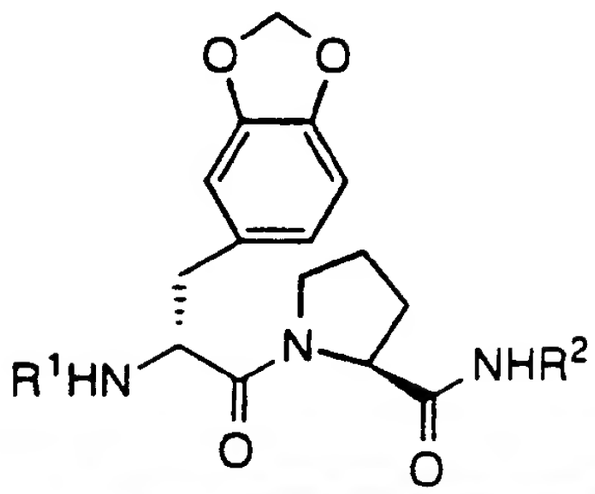
R^1	R^2
$CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-CH_2-$	$-CH_2CH_2CH_2$ 
	$-CH_2CH_2CH_2$ 

TABLE 5



R^1	R^2
$(CH_3)_3C-O-C(=O)-CH_2-$	$-CH_2$-(2-amino-4-pyridyl)
$(CH_3)_3C-N(H)-C(=O)-CH_2-$	$-CH_2$-(2-amino-4-pyridyl)
$(CH_3-CH_2)_2N-C(=O)-CH_2-$	$-CH_2$-(2-amino-4-pyridyl)
H	$-CH_2$-(2-amino-4-pyridyl)

TABLE 5



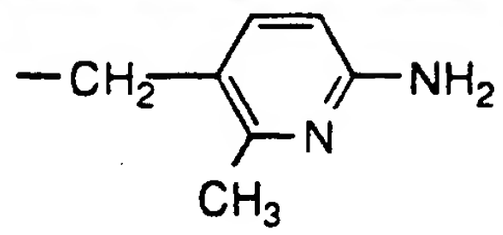
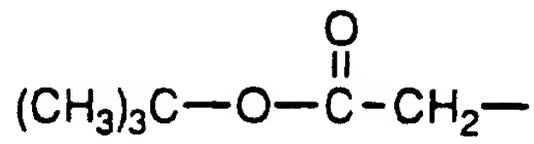
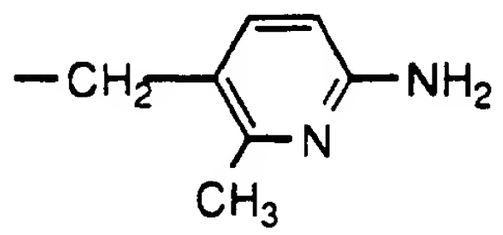
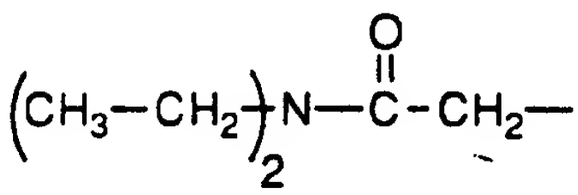
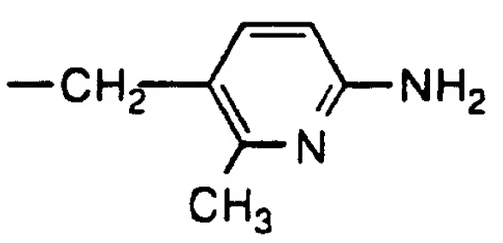
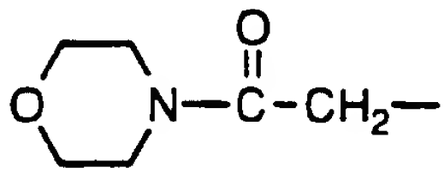
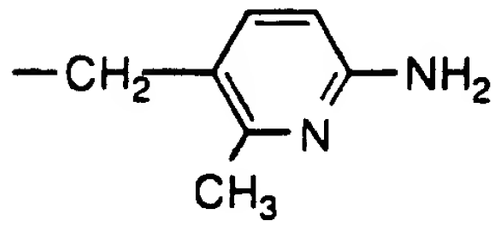
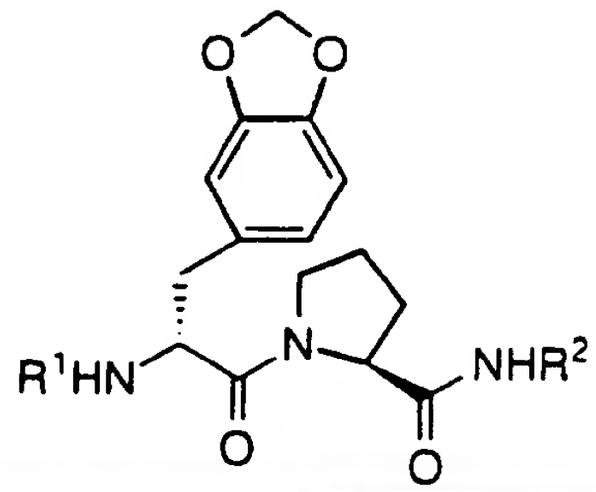
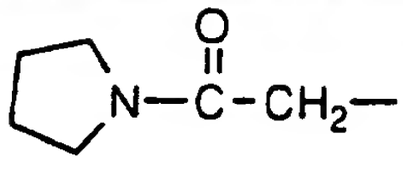
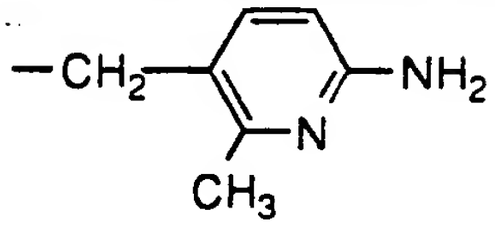
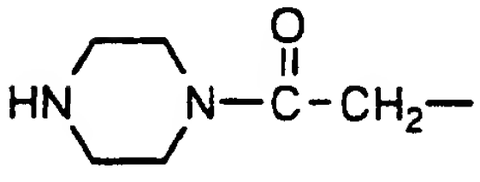
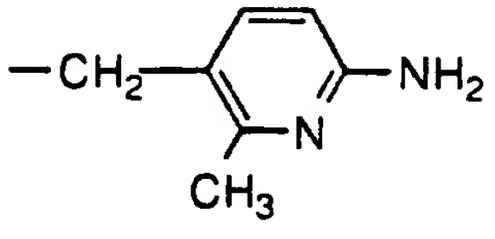
R^1	R^2
H	
	
	
	

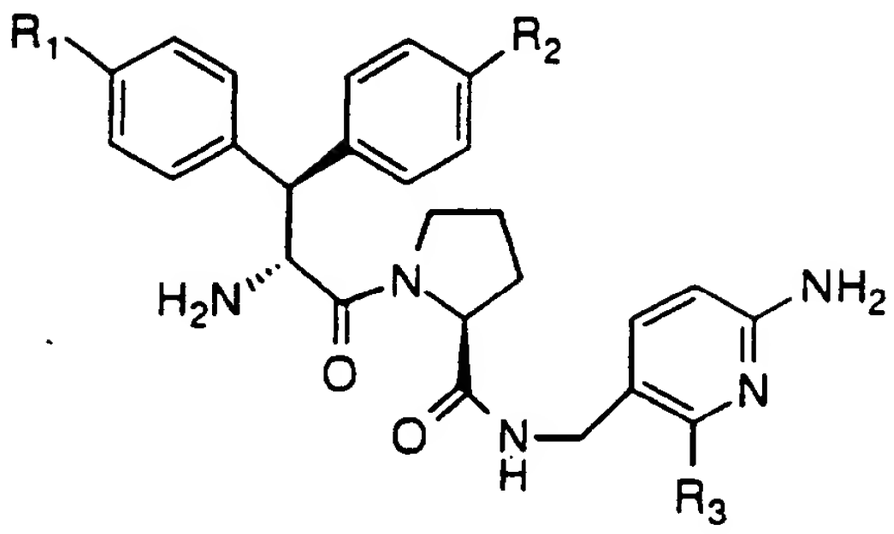
TABLE 5 (CONT'D)



R^1	R^2
	
	

5

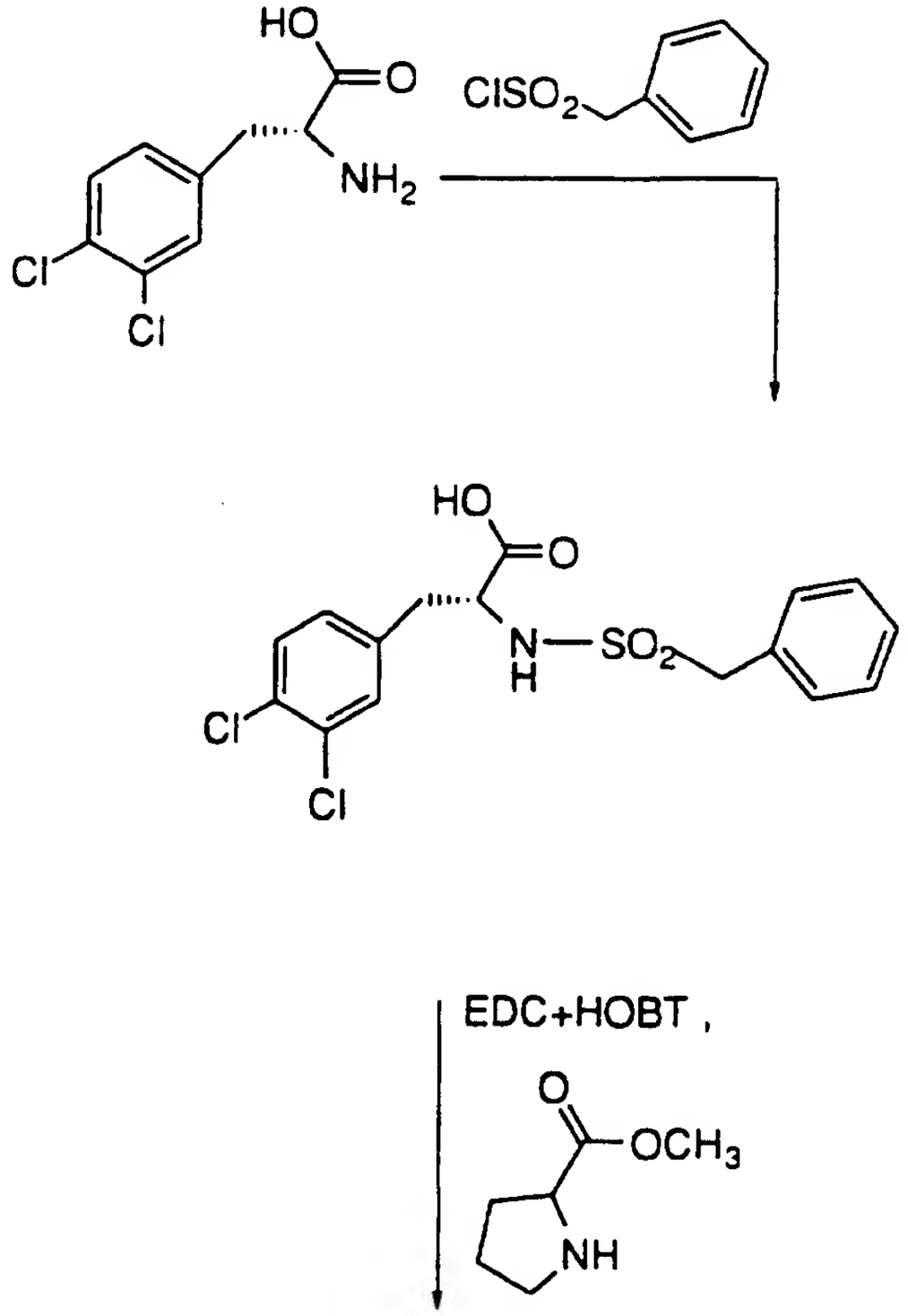
TABLE 6

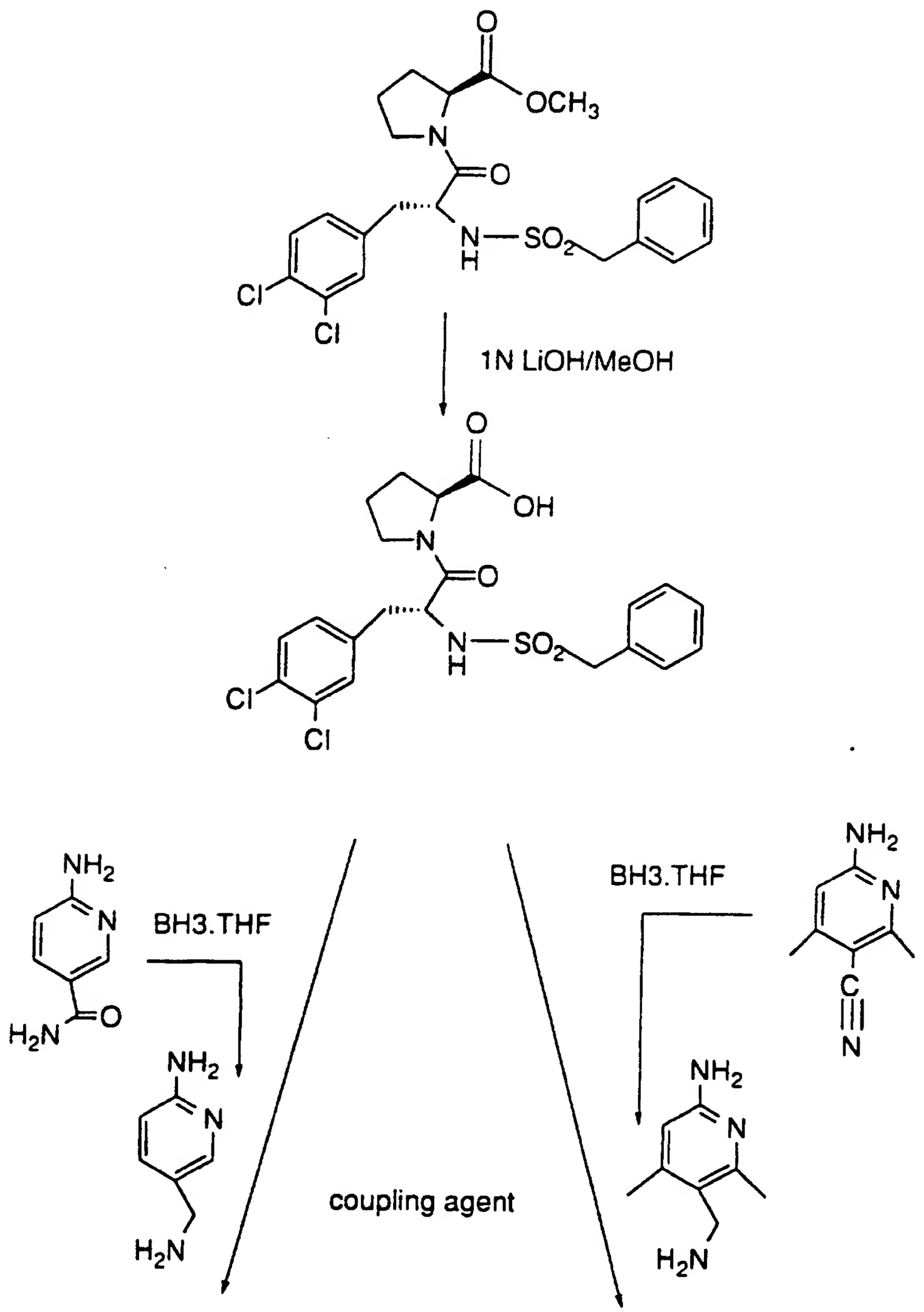


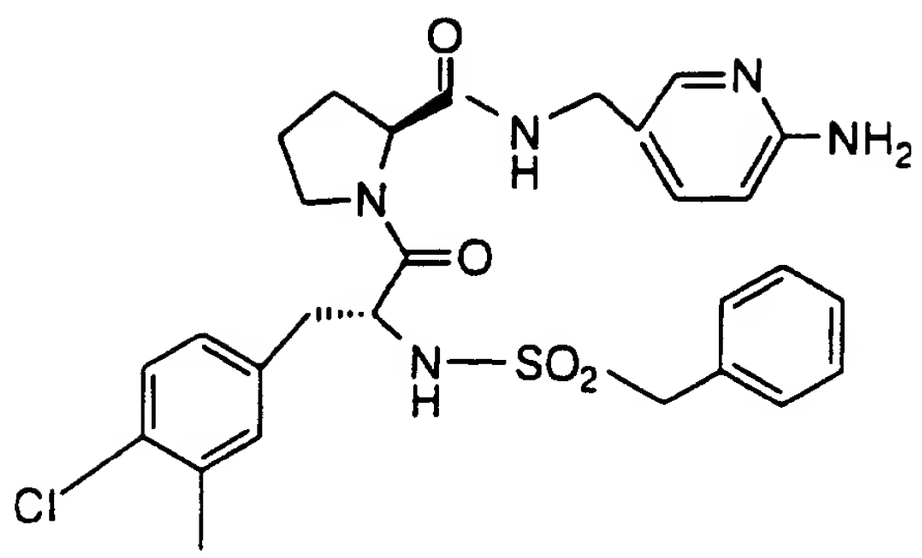
R_1	R_2	R_3
Cl	Cl	H
F	F	H
H	H	CH_3
Cl	Cl	CH_3
F	F	CH_3

Compounds of the invention can be prepared according to the general procedures outlined below:

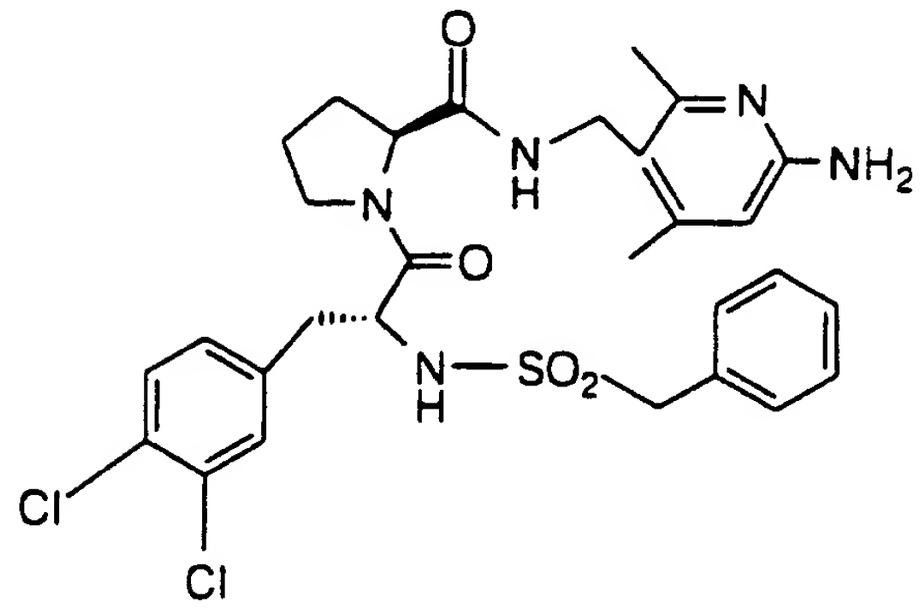
SCHEME 1



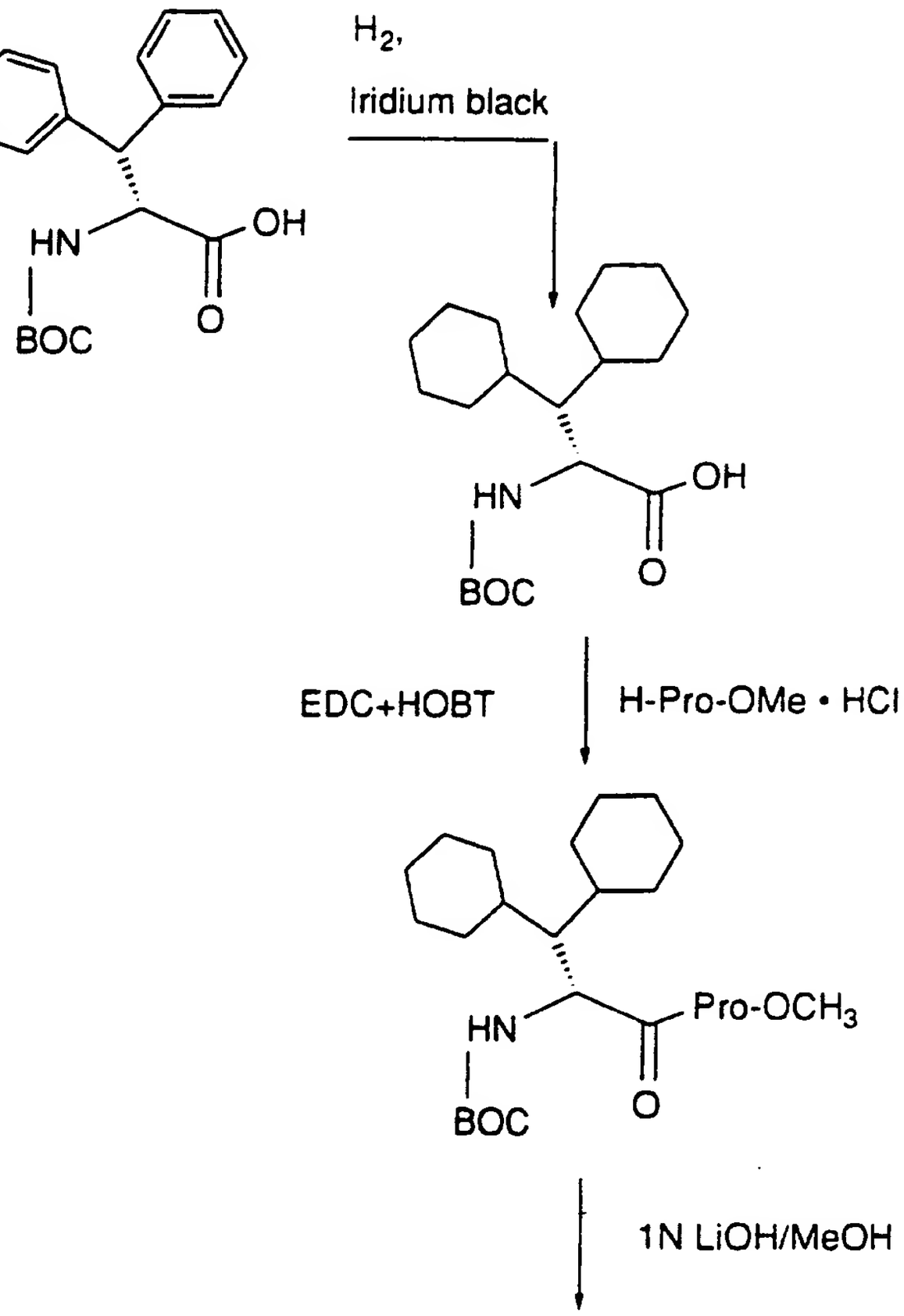

OCH3
N
O
N
H
SO2
Cl
Cl
1N LiOH/MeOH
OH
NH2
BH3.THF
H2N
coupling agent
C
N

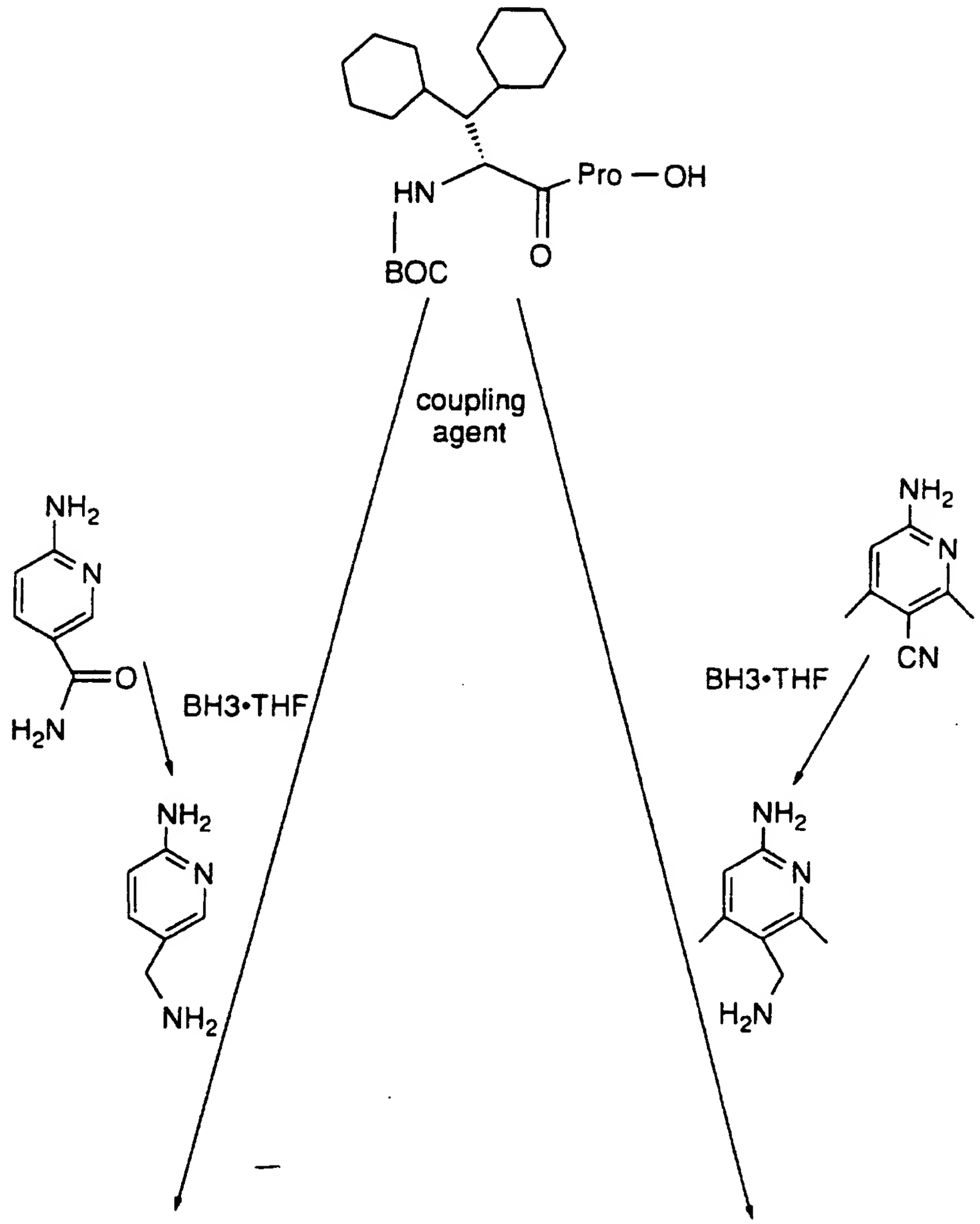


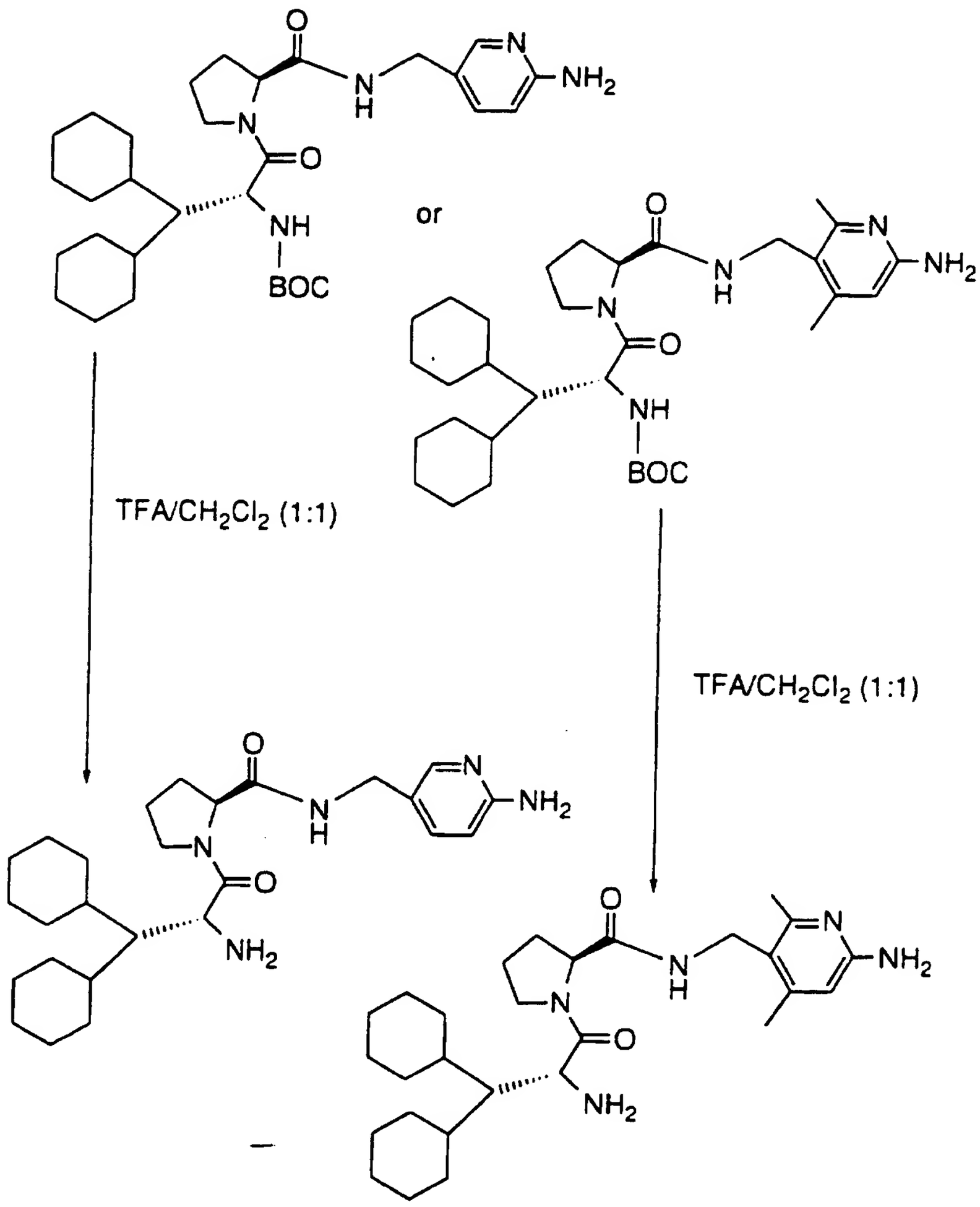
or



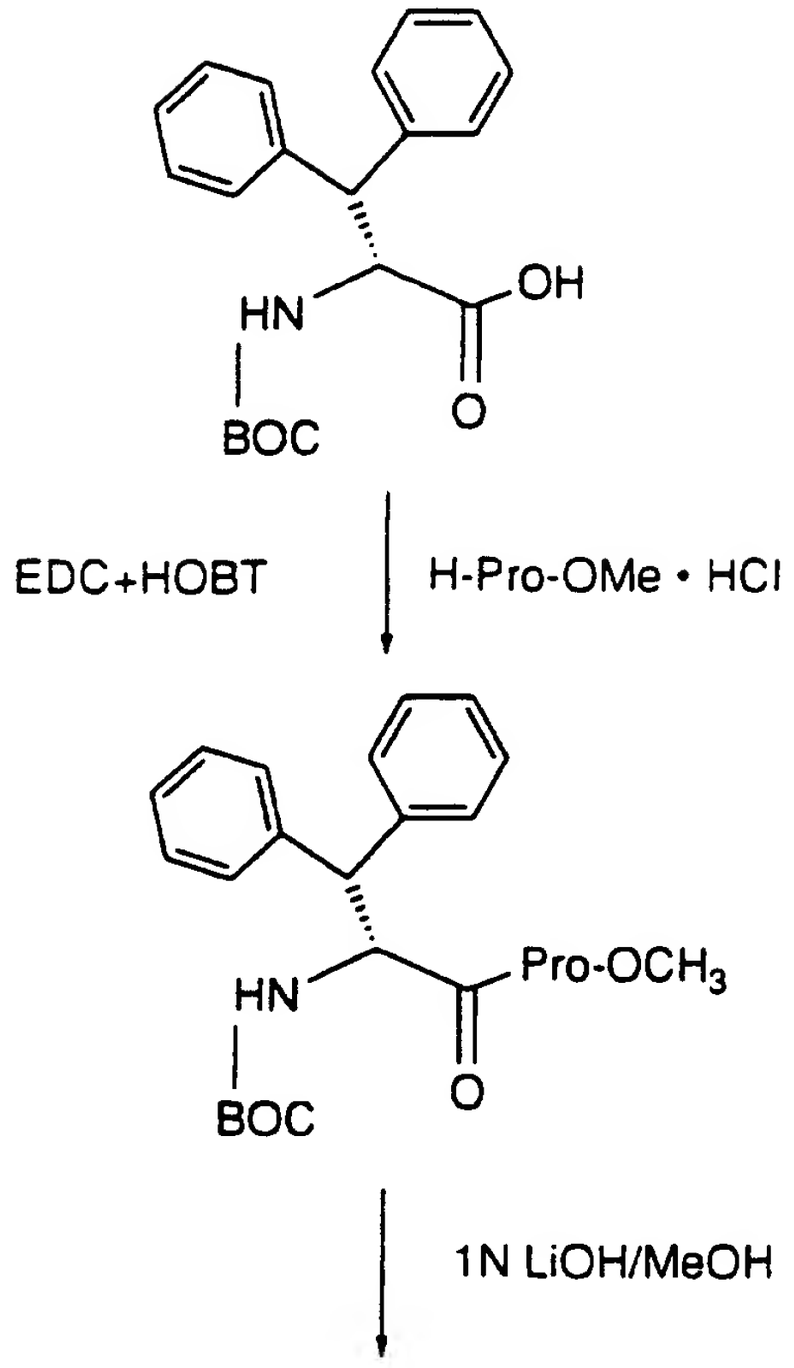
SCHEME 2

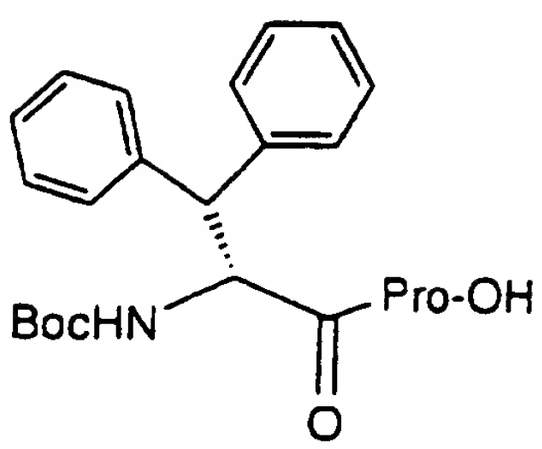

H_2,
Iridium black
HN
OH
O
BOC
EDC+HOBT
H-Pro-OMe • HCl
Pro-OCH_3
1N LiOH/MeOH


HN
Pro —OH
O
BOC
coupling agent
NH2
N
O
H2N
BH3•THF
NH2
N
NH2
NH2
N
CN
BH3•THF
NH2
N
H2N


or
TFA/CH2Cl2 (1:1)
TFA/CH2Cl2 (1:1)
NH2
BOC

SCHEME 3

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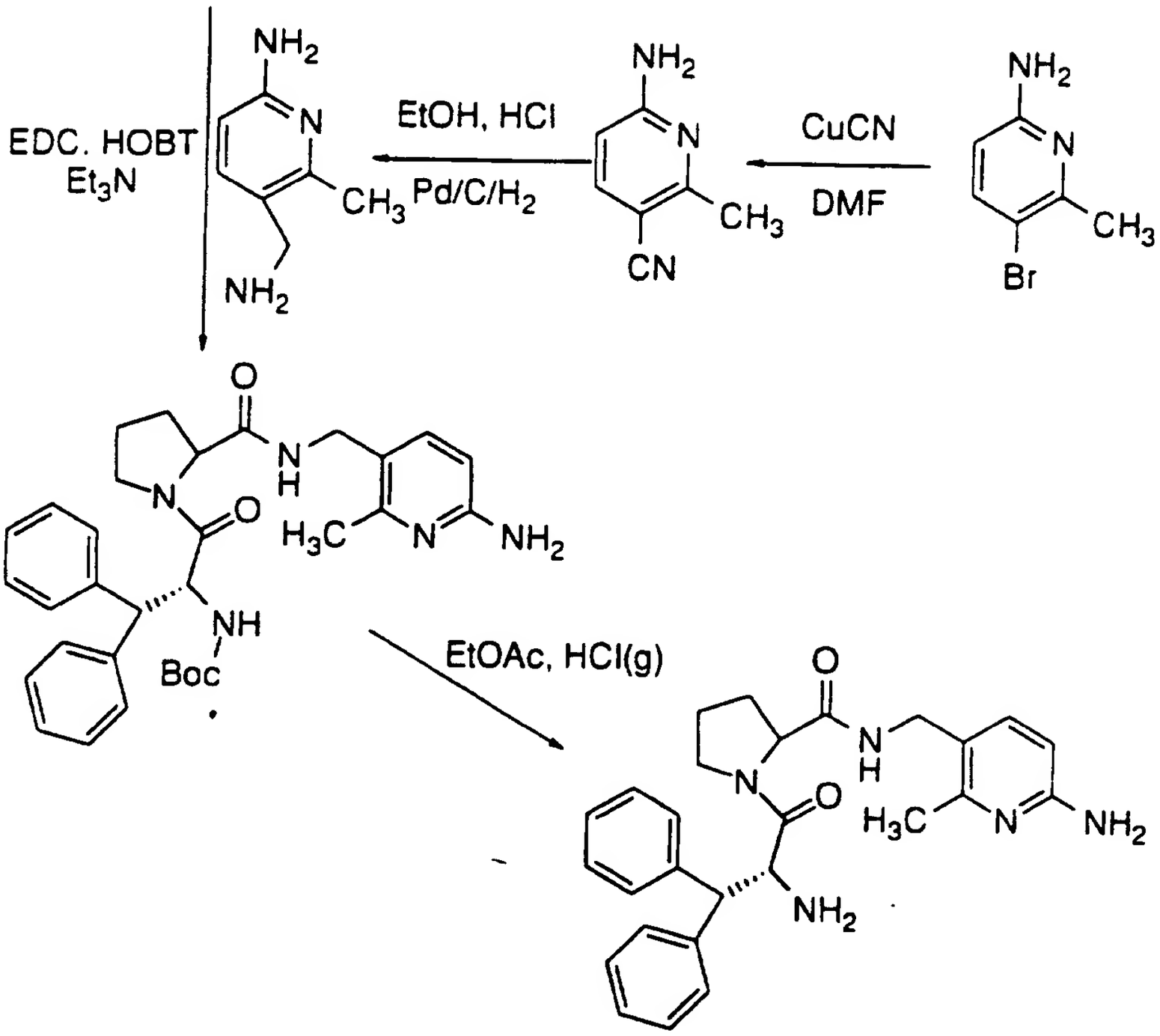
O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EtOH, HCl
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CuCN
DMF
NH2
CH3
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O
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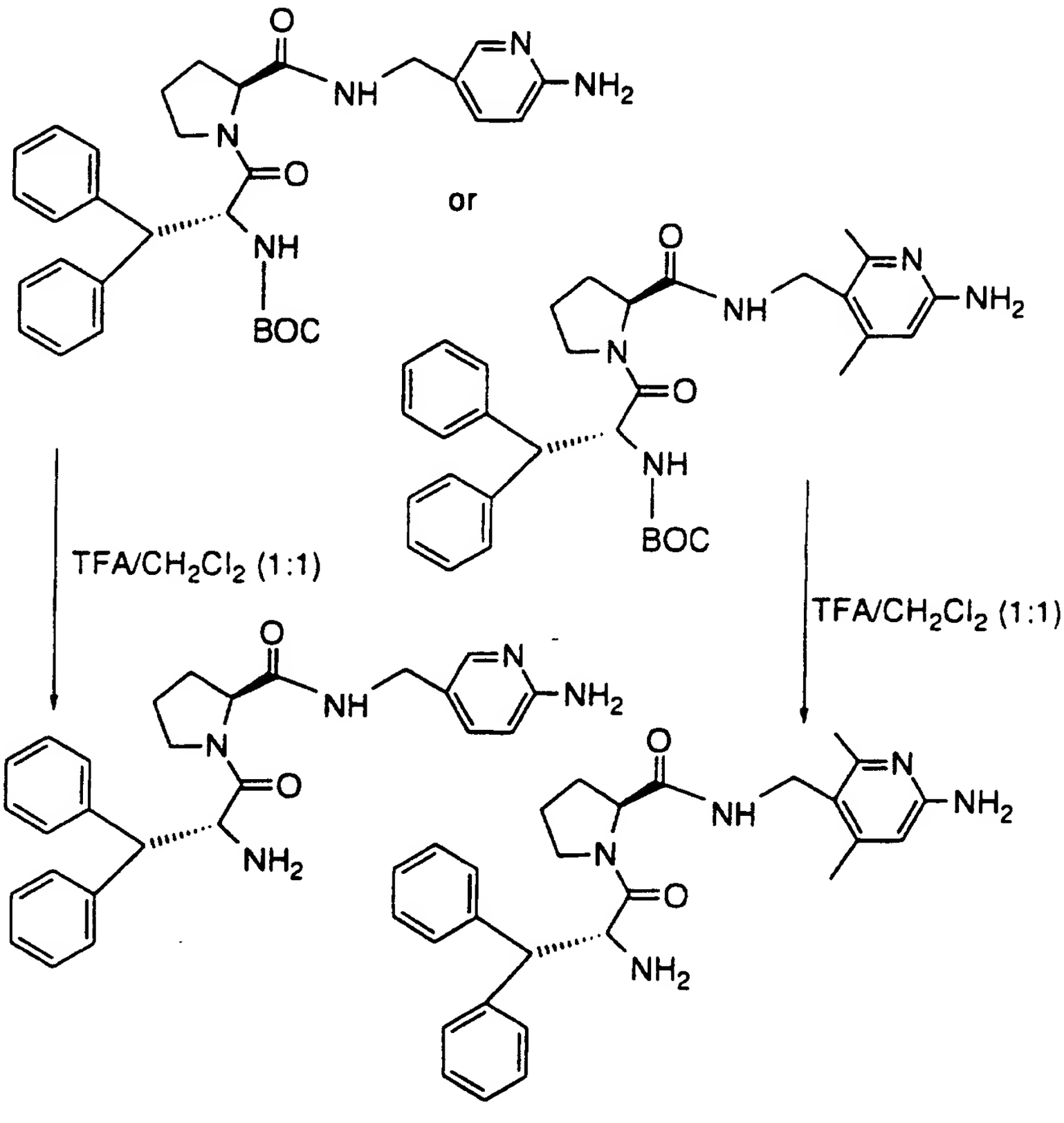
H3C
Boc
EtOAc, HCl(g)


or
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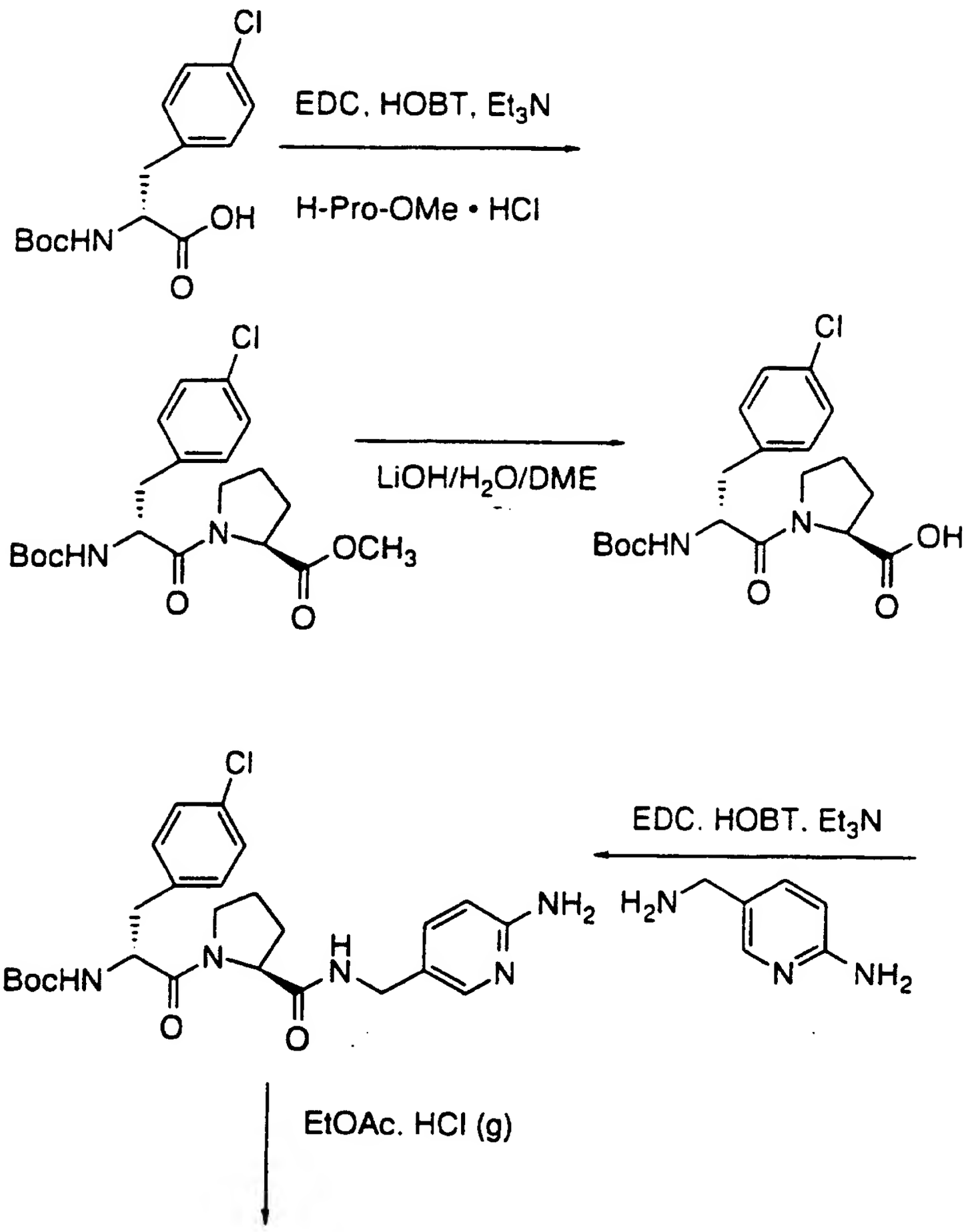
TFA/CH2Cl2 (1:1)
NH
NH2
BOC

SCHEME 4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Cl
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OCH3
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LiOH/H2O/DME
Cl
BocHN
N
OH
O
O
Cl
EDC. HOBT. Et3N
BocHN
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H
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H2N
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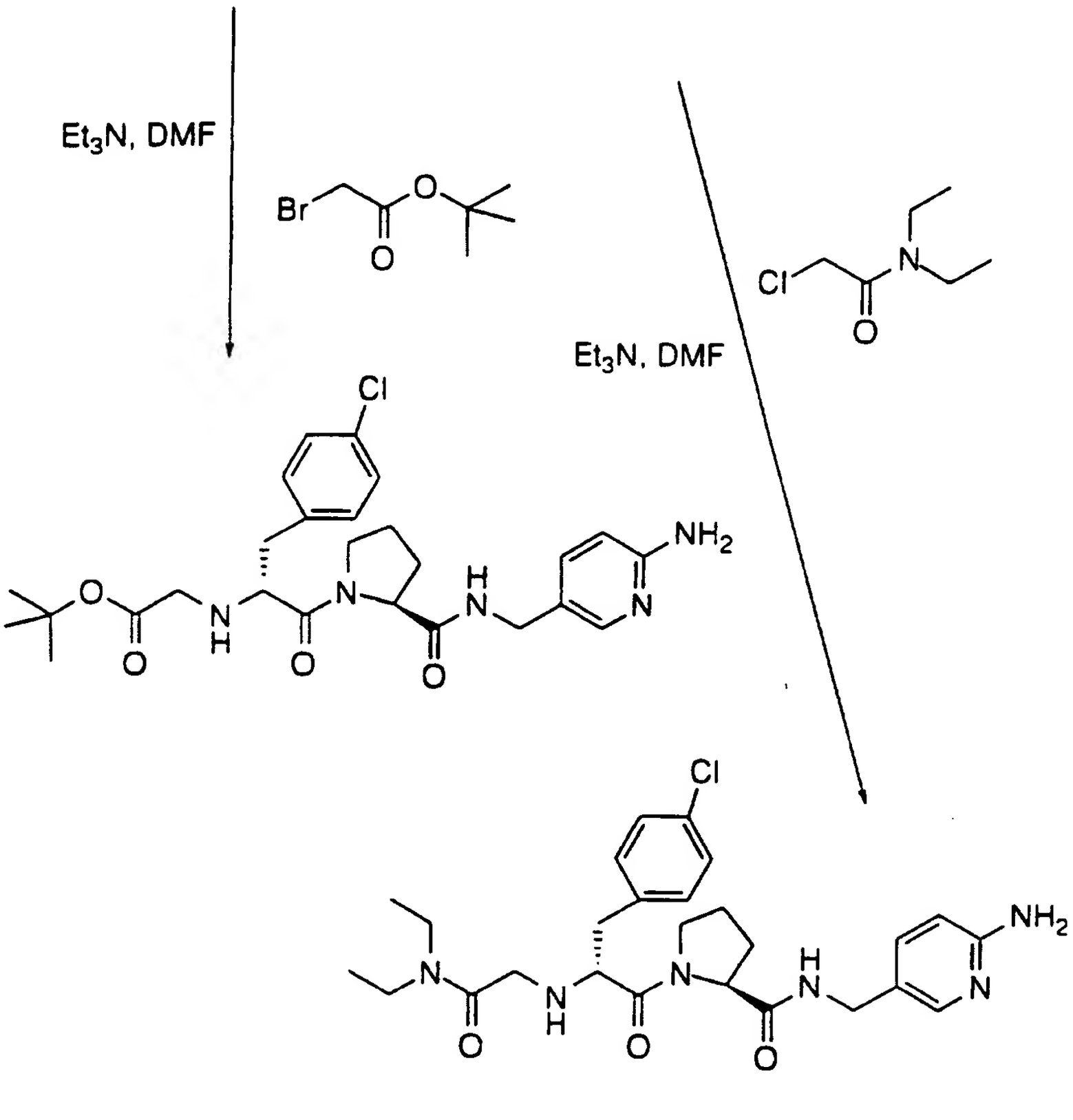
NH2
O
O
EtOAc. HCl (g)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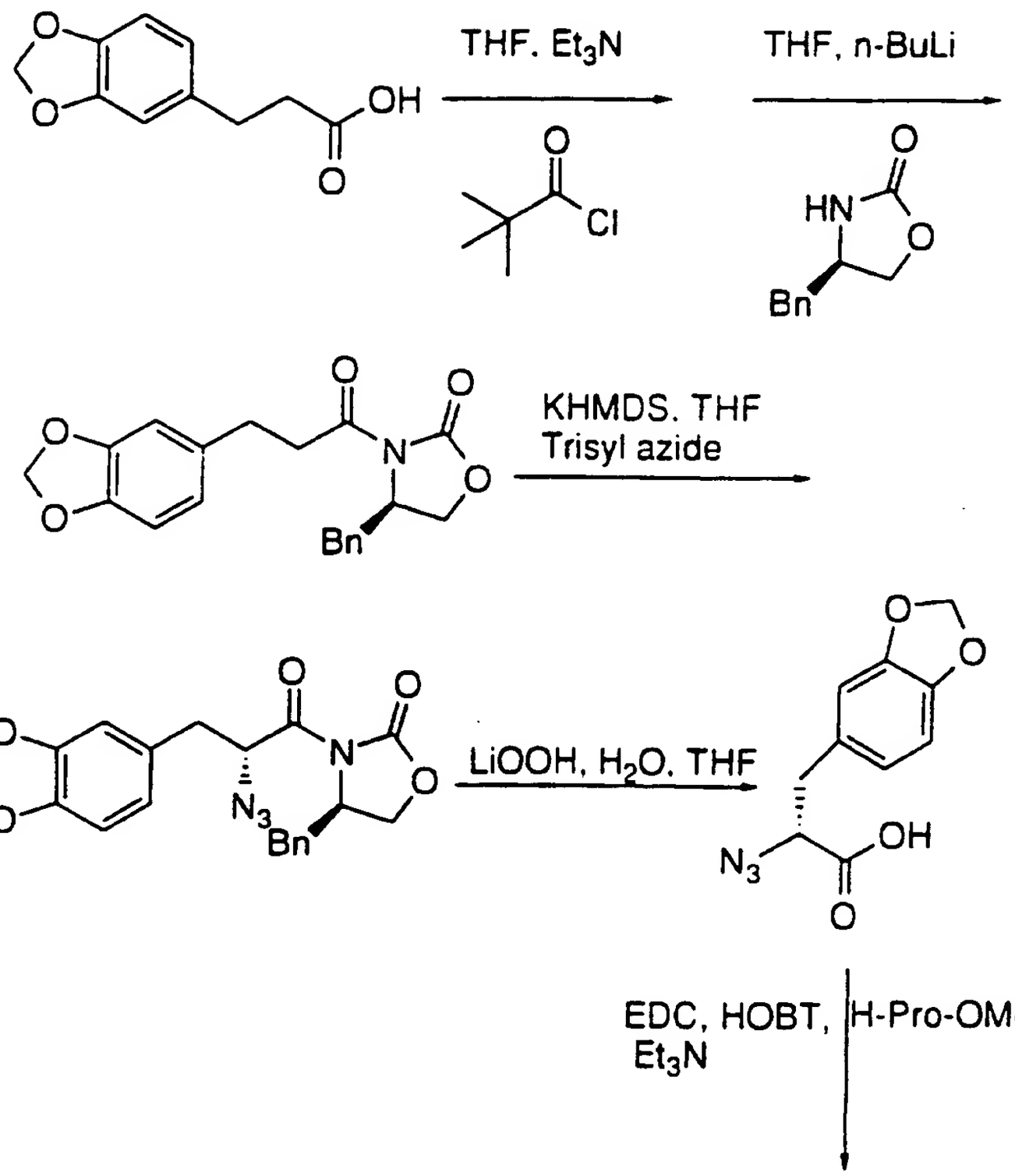
SCHEME 5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Bn
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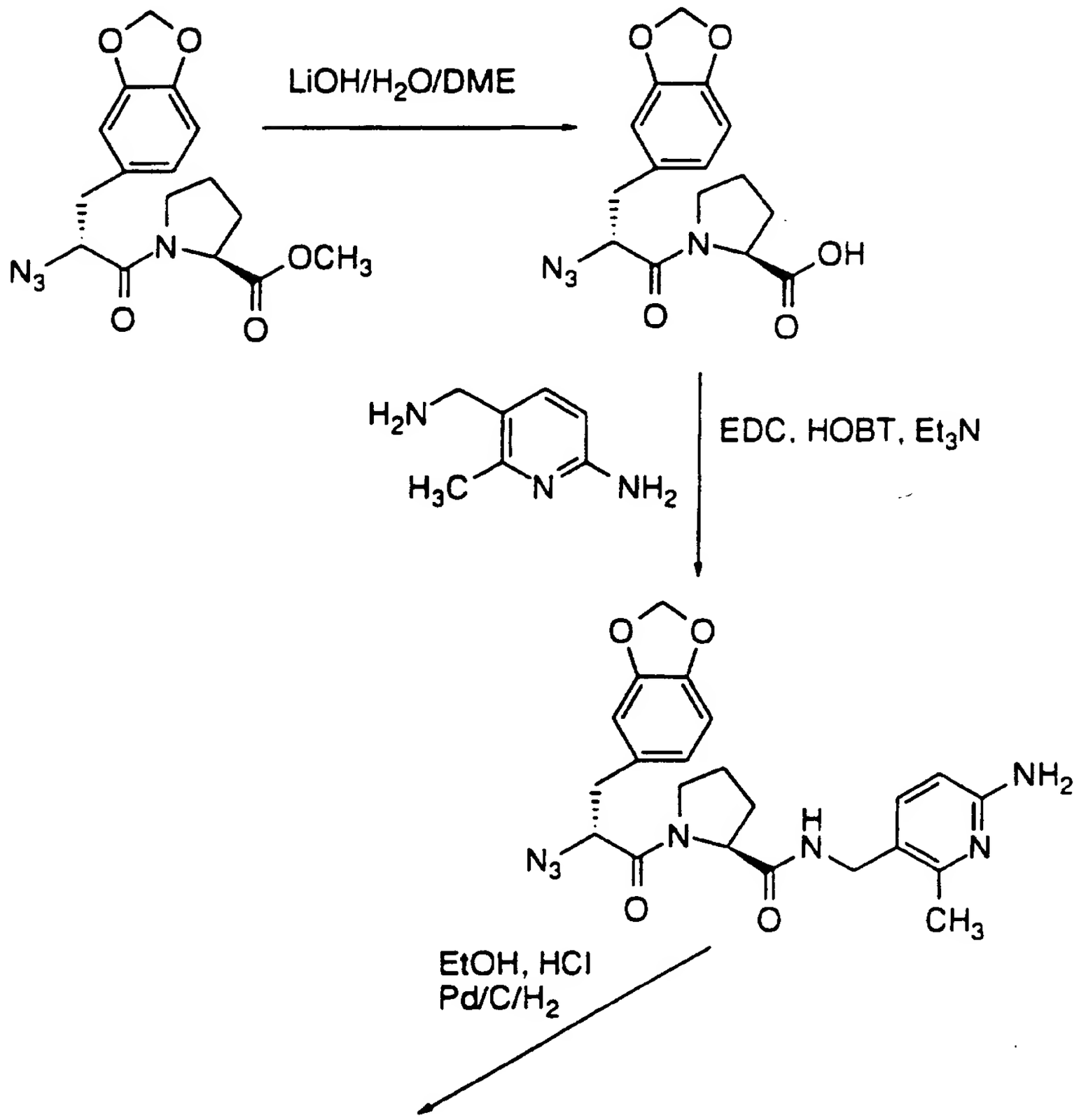
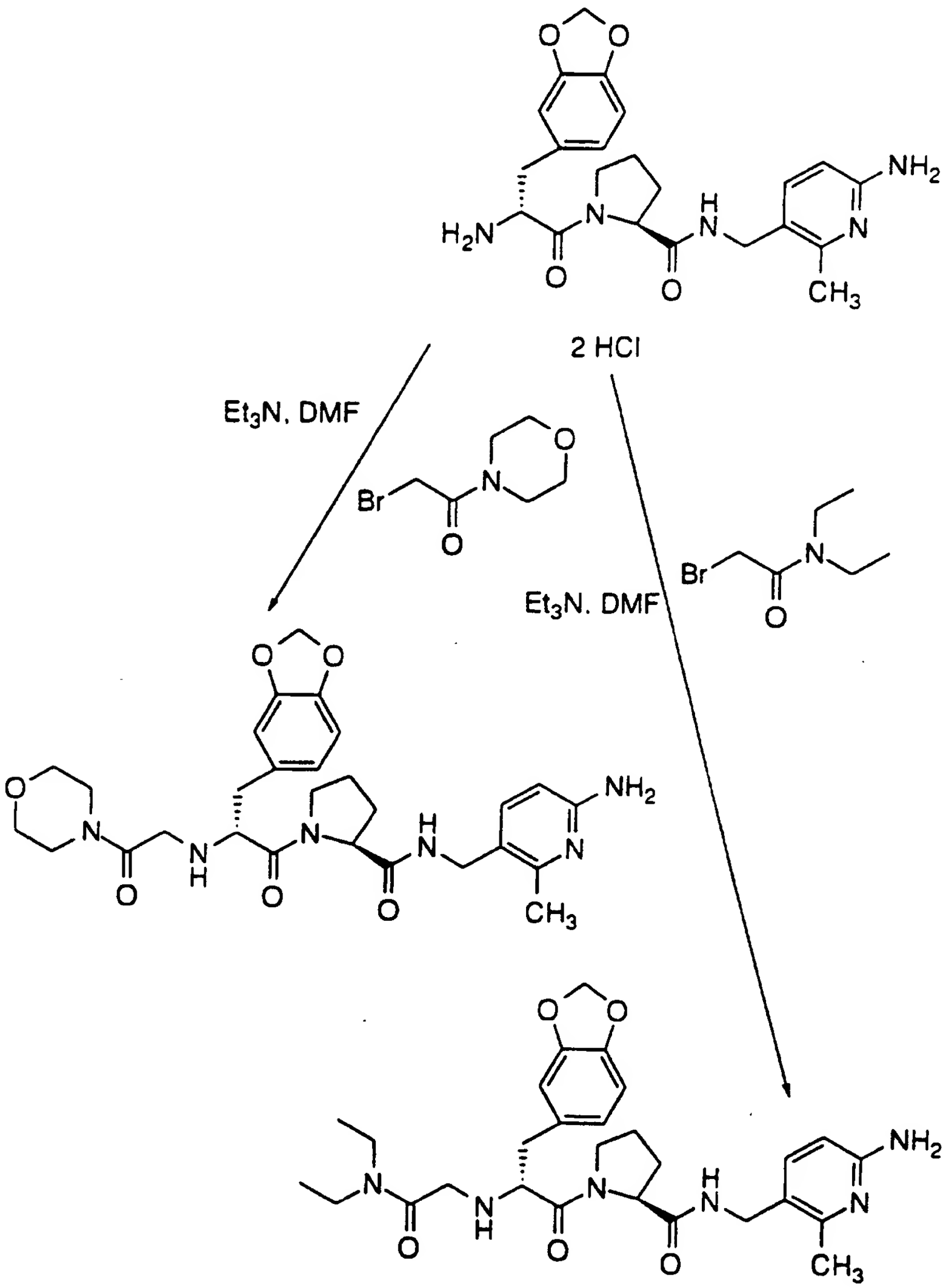
SCHEME 5 (CONT'D)



SCHEME 5 (CONT'D)



EXAMPLE 1

Preparation of BOC-D-3,3-Dicyclohexylalanyl-6-(aminopyridin-3-yl)methyl-L-prolineamide

Step A: Preparation of 6-Amino-3-aminomethylpyridine

A 300-ml flask was dried in an oven and cooled down in a dry nitrogen atmosphere. The flask was equipped with a rubber syringe cap and a magnetic stirring bar. The flask was immersed in a ice-water bath . and 21 ml (21 mmole) of 1.0M borane solution in THF was introduced into the reaction flask, followed by 0.3 ml of THF. Then 6-Aminonicotinamide (420 mg, 3.06 mmole) in 10 ml of THF was introduced. The resulting mixture was stirred for 10 min. and 5 ml of 6N HCl was added slowly, and then 15.0 ml of H_2O and 100 ml of MeOH was introduced, and stirred continually over night, and filtered, evaporated *in vacuo* to give product as a white solid which was further purified by chromatography using two columns of 40 g silica gel 60 (E. Merck) each and eluting with n-Butanol-HOAC-H_2O (4:1:2); Fractions containing product were combined to give 285 mg (76% yield) of product.

EI^+: 123

TLC: R_f=0.51, silica gel, n-Butanol-HOAC-H_2O (4:1:2);

Step B: Boc-D-3,3-Dicha-OH (1-2)

A solution of BOC-D-3,3-Diphe-OH (2.0 g, 5.8 mmol) in 50 ml acetic acid/10 ml H_2O was hydrogenated at 62 psi on a Parr apparatus over 400 mg of Ir black catalyst. After 24 h, a second portion of catalyst was added and the reaction continued for a second 24 h interval. The reaction was filtered through a Celite pad, and the filtrate was added with 150 ml of H_2O and filtrated again to give 2.0 g of BOC-D-3,3-Dicha as white solid (97% yield).

FABMS: 354

HPLC: retention time 24.3 min; C_{18}, 95%A to 5%A over 30 min, A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

Step C: Boc-D-3,3-Dicha-Pro-OMe (1-3)

To a solution of Boc-D-3,3-Dicha-OH (1.77 g, 5.0 mmol) and H-Pro-OMe•HCl (0.91 g, 5.5 mmol) in 12 ml of DMF was added 4.6 g (6.0 mmol) of HOBt•H_2O, the pH of the solution was adjusted to 8 (moist narrow pH paper), and EDC (6.47 g, 6.76 mmol) was added with magnetic stirring. After 3.5 hrs the reaction was quenched by the addition of 10 ml of water. After keeping the mixture at room temperature for 5 hrs, the solvents were evaporated at reduced pressure and the residue was dissolved in EtOAc-H_2O. Aqueous $KHSO_4$ was added to this two-phase mixture and the layers were separated. The organic layer was extracted with $NaHCO_3$, saturated NaCl, and dried over $MgSO_4$. The solvent was evaporated to give product as a white solid which was further purified by chromatography using two columns of 600 g silica gel 60 (E. Merck) each and eluting with EtOAc-hexane (2:8). Fractions containing product were combined to give 2.26 g (97% yield) of product.

In a similar manner are prepared the following:

N-(benzylsulfonyl)-D-3,4-Dichloro-Phe-Pro-OMe (2-2), by coupling of N-(benzylsulfonyl)-D-3,4-Dichloro-Phe-OH (2-1) with H-Pro-OMe•HCl.

BOC-D-3, 3-Diphe-Pro-OMe (3-1), by coupling of Boc-D-3,3-Diphe-OH with H-Pro-OMe•HCl.

Step D: Boc-D-3,3-Dicha-Pro-OH

A sample of Boc-D-3.3-Dicha-Pro-OMe (1.76 g, 3.8 mmol) dissolved in 100 ml of 1:1(v/v) MeOH/H_2O was treated with 2.2 N LiOH (2.2 ml) in portions over 1.5 hrs, keeping the pH at 12-13. After 3.5 hrs, the reaction solution was adjusted to pH 7 with dilute $KHSO_4$ solution, 100 ml of EtOAc and 50 ml of H_2O were added, and the aqueous layer was further adjusted to pH 2 with $KHSO_4$ solution. The organic layer was separated and washed twice with 50% saturated NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo* to give 1.64 g, (96% yield).

FABMS: 451

HPLC: retention time 26.4 min; C_{18}, 95%A to 5%A over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

In a similar manner are prepared the following:
N-(benzylsulfonyl)-D-3,4-Dichloro-Phe-Pro-OH, by hydrolysis of N-(benzylsulfonyl)-D-3,4-Dichloro-Phe-OMe with LiOH.
BOC-D-3,3-Diphe-Pro-OH, by hydrolysis of Boc-D-3,3-Diphe-OMe with LiOH

Step E: Preparation of BOC-D-3,3-Dicyclohexylalanyl-6-(aminopyridin-3-yl)methyl-L-prolineamide

A solution of 113 mg (0.25 mmol) of Boc-D-3,3-Dicha-Pro-OH, 62 mg (0.50 mmol) of 6-Amino-3-aminomethylpyridine, 43 mg (0.28 mmol) of HOBT, 54 mg (0.28 mmol) of EDC in 1.7 ml anh. NMP was treated with DIEA to PH 8.5, and the resulting solution stirred at room temp. in an N_2 atmosphere for 8 h. The reaction was diluted with 3X its volume of water, and the suspension stirred vigorously at room temp. for 15 min. The suspension was filtered, the residue purified by preparative HPLC using a trifluroacetic acid (0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 135 mg (97%) of product as a trifluoroacetic acid hydrate salt.
Anal. CHN: $C_{31}H_{49}N_5O_4 \cdot 1.75\ CF_3CO_2H \cdot 0.90\ H_2O$.
FAB MS: M+1 = 556.
HPLC: 99% pure @214, retention times=22.7 min, (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min, A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 2

Preparation of D-3,3-Dicyclohexylalanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide

A solution of 122 mg (0.22 mmol) BOC-D-3,3-dicyclohexylalanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide in 10 ml of 50% TFA/CH_2Cl_2 was stirred for 20 min, and the TFA was

removed under reduced pressure and the product purified by preparative HPLC using a TFA(0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 96 mg (96%) of the title compound as a trifluoroacetic acid hydrate salt.

Anal. CHN: $C_{26}H_{41}N_5O_2 \cdot 2.70\ CF_3CO_2H \cdot 0.55\ H_2O$.

FAB MS: M+1 = 456.

HPLC: 99% pure @214. retention times=16.5 min. (Vydac C_{18}. gradient of 95%A/B to 5%A/B over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 3

Preparation of N-(benzylsulfonyl)-D-3,4-dichlorophenylalanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide

Step A: Preparation of N-(benzylsulfonyl)-D-3,4 -Cl_2Phe-OH(2-1)

(D)-3,4 -Cl_2PheOH (1.4 g. 6.0 mmol) was dissolved in 48 mL dioxane by addition of 6 ml 1N NaOH. The resulting solution was treated dropwise with phenylmethanesulfonyl chloride with rapid stirring at room temperature. After 2.5 hour. the aqueous layer was further adjusted to pH 2 with $KHSO_4$ solution. 150 ml of EtOAc were added. The organic layer was separated and washed twice with saturated NaCl solution. dried over Na_2SO_4. and evaporated *in vacuo* to give 2.31 g (80% yield).

FAB MS: M+1 = 485

HPLC: 97% pure @214. retention times=20.1 min. (Vydac C_{18}. gradient of 95%A/B to 5%A/B over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

Step B: Preparation of N-(benzylsulfonyl)-D-3,4-dichlorophenyl-alanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide

A solution of 121 mg (0.25 mmol) of N-(benzylsulfonyl)-D-3,4-Cl_2Phe-Pro-OH, 62 mg (0.50 mmol) of 6-Amino-3-aminomethylpyridine, 43 mg (0.28 mmol) of HOBT. 54 mg (0.28

mmol) of EDC in 1.7 ml anh. NMP was treated with DIEA to pH 8.5, and the resulting solution stirred at room temp. in an N_2 atmosphere for 8 h. The reaction was diluted with 3X its volume of water, and the suspension stirred vigorously at room temp. for 15 min. The suspension was filtered, the residue purified by preparative HPLC using a trifluroacetic acid (0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 140 mg (95%) of product as a trifluoroacetic acid hydrate salt.

Anal. CHN: $C_{27}H_{29}N_5O_4S_1Cl_2 \cdot 2.35\ CF_3CO_2H \cdot 0.95\ H_2O$.

FAB MS: M+1 = 590.

HPLC: 99% pure @214, retention times=18.8 min. (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 4

Preparation of N-BOC-D-3,3-diphenylalanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide

110 mg, 0.25 mmol of N-BOC-D-3,3-Diphe-Pro-OH and 130 mg, 0.50 mmol of 6-Amino-3-aminomethylpyridine were coupled with hydroxybenztriazole hydrate (43 mg, 0.28 mmol) and EDC-HCl (54 mg, 0.28 mmol) in 1.5 mL DMF at pH 8.5 with DIEA. The mixture was stirred under N_2 at room temperature overnight, then diluted with 10 mL of 10% aqueous citric acid and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with aqueous Na_2CO_3, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude Boc derivative of the title compound, and the product purified by preparative HPLC using a TFA(0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 122 mg (90%) of the white powder as a trifluoroacetic acid hydrate salt.

Anal.CHN: $C_{31}H_{37}N_5O_4 \cdot 1.75\ CF_3CO_2H \cdot 1.05\ H_2O$.

FAB MS: M+1 = 544.

HPLC: 99% pure @214, retention times=18.8 min. (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min, A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 5

Preparation of D-3,3-diphenylalanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide

A solution of (109 mg, 0.20 mmol) N-BOC-D-3,3-diphenylalanyl-N-(6-aminopyridin-3-yl)methyl-L-prolineamide in 10 ml of 50% TFA/CH_2Cl_2 was stirred for 20 min. the TFA was removed under reduced pressure, and the product purified by preparative HPLC using a TFA(0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 87 mg (98%) of the title compound as a trifluoroacetic acid hydrate salt.

Anal.CHN: $C_{26}H_{29}N_5O_2 \cdot 2.80\ CF_3CO_2H \cdot 1.35\ H_2O$.

FAB MS: M+1 = 444.

HPLC: 99% pure @214, retention times=13.9 min. (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 6

Preparation of BOC-D-3,3-Dicyclohexylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-prolineamide

Step A: Preparation of 6-Amino-2,4-dimethyl-3-amino-methylpyridine

A 300-ml flask was dried in an oven and cooled down in a dry nitrogen atmosphere. The flask was equipped with a rubber syringe cap and a magnetic stirring bar. The flask was immersed in a ice-water bath, and 21 ml (21 mmole) of 1.0M borane solution in THF was introduced into the reaction flask, followed by 0.3 ml of THF. Then 6-Amino-2,4-dimethyl-3-pyridinecarbonitrile (442 mg, 3.0 mmole) in 10

ml of THF was introduced. The resulting mixture was stirred for 10 min, and 5 ml of 6N HCl was added slowly, and then 15.0 ml of H_2O and 100 ml of MeOH was introduced, and stirred continually over night, and filtered, filtrate was evaporated *in vacuo* to give product as a white solid which was further purified by chromatography using a columns of 40 g silica gel 60 (E. Merck) and eluting with n-Butanol-HOAC-H_2O (4:1:2). Fractions containing product were combined to give 407 mg (90% yield).

EI^+: 51

TLC: R_f=0.73, silica gel, n-Butanol-HOAC-H_2O (4:1:2)

Step B: Preparation of BOC-D-3,3-Dicyclohexylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-prolineamide

A solution of 113 mg (0.25 mmol) of Boc-D-3,3-Dicha-Pro-OH, 75.5 mg (0.50 mmol) of 6-Amino-2,4-dimethyl-3-aminomethylpyridine (1-1), 43 mg (0.28 mmol) of HOBT, 54 mg (0.28 mmol) of EDC in 1.7 ml anh. NMP was treated with DIEA to PH 8.5, and the resulting solution stirred at room temp. in an N_2 atmosphere for 8 h. The reaction was diluted with 3X its volume of water, and the suspension stirred vigorously at room temp. for 15 min. The suspension was filtered, the residue purified by preparative HPLC using a trifluroacetic acid (0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 135 mg (93%) of product as a trifluoroacetic acid hydrate salt.

Anal. CHN: $C_{33}H_{53}N_5O_4 \cdot 1.55\ CF_3CO_2H \cdot 0.80\ H_2O$.

FAB MS: M+1 = 584.

HPLC: 99% pure @214, retention times=23.2 min, (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min, A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 7

Preparation of D-3,3-Dicyclohexylalanyl-N-(6-amino-2,4-dimethyl-pyridin-3-yl)methyl-L-prolineamide

A solution of 128 mg (0.22 mmol) N-BOC-D-3,3-Dicyclohexylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-prolineamide in 10 ml of 50% TFA/CH_2Cl_2 was stirred for 20 min. and the TFA was removed under reduced pressure and the product purified by preparative HPLC using a TFA(0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 102 mg (96%) of the title compound as a trifluoroacetic acid hydrate salt.

Anal.CHN: $C_{28}H_{45}N_5O_2 \cdot 2.50\ CF_3CO_2H \cdot 1.35\ H_2O$.

FAB MS: M+1 = 484.

HPLC: 99% pure @214. retention times=16.7 min. (Vydac C18. gradient of 95%A/B to 5%A/B over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 8

Preparation of N-(benzylsulfonyl)-D-3,4-dichlorophenylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-proline amide

A solution of 121 mg (0.25 mmol) of N-(benzylsulfonyl)-D-3,4-Cl_2Phe-Pro-OH, 75.5 mg (0.50 mmol) of 6-Amino-2,4-dimethyl-3-aminomethylpyridine, 43 mg (0.28 mmol) of HOBT. 54 mg (0.28 mmol) of EDC in 1.7 ml anh. NMP was treated with DIEA to pH 8.5. and the resulting solution stirred at room temp. in an N_2 atmosphere for 8 h. The reaction was diluted with 3X its volume of water. and the suspension stirred vigorously at room temp. for 15 min. The suspension was filtered, the residue purified by preparative HPLC using a trifluroacetic acid (0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 140 mg (95%) of white solid as a trifluoroacetic acid hydrate salt.

Anal. CHN: $C_{29}H_{33}N_5O_4S_1Cl_2 \cdot 1.65\ CF_3CO_2H \cdot 0.60\ H_2O$.

FAB MS: M+1 = 618.

HPLC: 99% pure @214, retention times=19.5 min. (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min, A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 9

Preparation of N-BOC-D-3,3-diphenylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-proline amide

108 mg, 0.25 mmol of N-BOC-D-3,3-Diphe-Pro-OH and 75.5 mg, 0.50 mmol of 6-Amino-2,4-dimethyl-3-aminomethylpyridine were coupled with hydroxybenztriazole hydrate (43 mg, 0.28 mmol) and EDC-HCl (54 mg, 0.28 mmol) in 1.5 mL DMF at PH 8.5 with DIEA. The mixture was stirred under N_2 at room temperature overnight, then diluted with 10 mL of 10% aqueous citric acid and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with aqueous Na_2CO_3, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude Boc derivative of the title compound, and the product purified by preparative HPLC using a TFA(0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 128 mg (90%) of the white powder as a trifluoroacetic acid hydrate salt.

Anal. CHN: $C_{33}H_{41}N_5O_4 \cdot 1.35\ CF_3CO_2H \cdot 1.55\ H_2O$.

FAB MS: M+1 = 572.

HPLC: 99% pure @214, retention times=19.3min. (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min, A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 10

Preparation of D-3,3-diphenylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-proline amide

A solution of (114 mg, 0.20 mmol) N-BOC-D-3,3-diphenylalanyl-N-(6-amino-2,4-dimethylpyridin-3-yl)methyl-L-proline amide in 10 ml of 50% TFA/CH_2Cl_2 was stirred for 20 min, and the TFA was removed under reduced pressure and the product purified by

preparative HPLC using a TFA(0.1%)-CH_3CN gradient. Lyophilization of pure fractions gave 92 mg (98%) of the title compound as a trifluoroacetic acid hydrate salt.

Anal.CHN: $C_{28}H_{33}N_5O_2 \cdot 2.75\ CF_3CO_2H \cdot 2.90\ H_2O$.

FAB MS: M+1 = 472.

HPLC: 99% pure @214, retention times=14.2 min. (Vydac C_{18}, gradient of 95%A/B to 5%A/B over 30 min. A=0.1%TFA-H_2O, B=0.1%TFA-CH_3CN

EXAMPLE 11

Preparation of N-(t-butyloxy-carboxymethyl)-D-4-chlorophenyl-alanyl-N-(6-aminopyridin-3-yl)methyl-L-proline amide

Step A: Preparation of 6-amino-3-(aminomethyl)pyridine

To 6-aminonicotinamide (11.0 g, 80.21 mmol) suspended in 500 mL of THF was added solid lithium aluminum hydride (6.35 g, 167.3 mmol) portionwise. This mixture was refluxed for 72 h, cooled to RT and quenched by the addition of water (4.71 mL), 1N NaOH (4.71 mL) and then water (19 mL). After 1 h of vigorous stirring the mixture was filtered through celite and washed with 500 mL of THF:MeOH (85:15). The volatiles were removed *in vacuo* and the solid was purified by flash column chromatography (60 x 150 mm column of SiO_2, EtOH/NH_4OH gradient elution 99:1, 98:2 97:3) to afford 3.70 g (37% yield) of a white solid: TLC (EtOH:NH_4OH, 99:1) R_f = 0.16; ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (br s, 2H), 3.73 (s, 2H), 4.50 (br s, 2H), 6.48 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 8.3 and 2.3 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H).

Step B: Preparation of N-Boc-D-4-chlorophenylalanyl-L-proline methyl ester

To a solution of N-Boc-D-4-chlorophenylalanine (2.72 g, 9.07 mmol), L-proline methyl ester hydrochloride (1.50 g, 9.07 mmol), EDC (2.08 g, 10.884 mmol), and HOBt (1.51 g, 10.884 mmol) in 15

mL of DMF at 0°C was added triethylamine (3.0 mL, 21.76 mmol). This stirred 1 h at 0°C then 15 h at RT and was diluted with 200 mL of ethyl acetate and washed with sat'd $NaHCO_3$ (1 x 25 mL), water (5 x 25 mL), and brine (1 x 20 mL). The solution was dried over $MgSO_4$, filtered and concentrated to an oil which was purified by flash column chromatography (40 x 150 mm column of SiO_2, EtOAc:Hex gradient elution 1:2. to 1:1,) to afford 3.24 g (87% yield) of a white foam: TLC (EtOAc:Hex. 2:1) $R_f = 0.68$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.61-1.66 (m, 1H), 1.88-2.02 (m, 3H), 2.84-3.02 (m, 3H), 3.58-3.67 (m, 1H), 3.72 and 3.72 rotomers (s, 3H), 4.31 (dd, J = 7.7 and 3.5 Hz, 1H), 4.62 (dd, J = 14.6 and 8.3 Hz, 1H), 5.31 (d, J = 8.4 Hz, 1H), 7.08-7.15 (m, 2H), 7.23-7.26 (m, 2H).

Step C: Preparation of N-Boc-D-4-chlorophenylalanyl-L-proline carboxylic acid

To a solution of N-Boc-D-4-chlorophenylalanyl-L-proline methyl ester (4.98 g, 12.12 mmol) in 45 mL of DME was added LiOH (1.16 g) dissolved in 15 mL of water. After 0.5h the solution was concentrated to 15 mL acidified to pH 3 with 10% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide 5.05 g of a white foam : TLC (EtOAc:Hex, 2:1) $R_f = 0.05$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.69-1.80 (m, 2H), 1.88-1.94 (m, 1H), 2.09 (s, 1H), 2.20-2.25 (m, 1H), 2.77-2.83 (m, 1H), 2.92-2.99 (m, 2H), 3.55-3.63 (m, 1H), 4.37 (d, J = 5.8 Hz, 1H), 4.62-4.64 (m, 1H), 5.38 (d, J = 6.2 Hz, 1H), 7.09-7.18 (m, 2H), 7.20-7.27 (m, 2H).

Step D: Preparation of 6-amino-3-(aminomethyl)pyridine-N-Boc-D-4-chlorophenylalanyl-L-proline amide

To a solution of N-Boc-D-4-chlorophenylalanine-L-proline carboxylic acid (1.22 g, 3.07 mmol) in 5 mL DMF was added 6-amino-3-(aminomethyl)pyridine (0.434 g, 3.53 mmol), HOBt (0.501 g, 3.684 mmol), and EDC (0.706 g, 3.684 mmol), cooled to 0°C and added

triethylamine (0.51 mL, 3.68 mmol). After 18 h the reaction mixture was concentrated, diluted into ethyl acetate (150 mL) and washed with saturated $NaHCO_3$ (1x20 mL), water (5x20 mL) and brine (1x15 mL), dried over $MgSO_4$, filtered and concentrated to an oil. Flash column chromatography (30x150 mm column of SiO_2, CH_2Cl_2/CH_2Cl_2 saturated with NH_3/MeOH gradient elution 60:39:1 to 60:38:2 to 60:35:5) provided 1.30 g of a yellowish foam: TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 60:35:5) Rf = 0.34; ^1H NMR (400 MHz, $CDCl_3$) d1.36 (s, 9H), 1.64-1.74 (m, 2H), 1.85 (br s, 1H), 2.25-2.27 (m, 1H), 2.74-2.87 (m, 1H), 2.89-2.99 (m, 2H), 3.64-3.66 (m, 1H), 4.17-4.31 (m, 2H), 4.42-4.50 (m, 4H), 5.25 (d, J = 3.8 Hz, 1H), 6.45 (dd, J = 8.3 and 1.9 Hz, 1H), 7.12 = 7.14 (m, 2H), 7.25 = 7.37 (m, 4H), 7.91 (s, 1H).

Anal.CHN: $C_{25}H_{32}N_5O_4Cl \cdot 0.2\ H_2O$.

Calc. C 59.38; H 6.46; N 13.85.

Found C 59.02; H 6.27; N 13.58.

Step E: Preparation of N-D-4-chlorophenyl-alanyl-N-(6-aminopyridin-3-yl)methyl-L-proline amide

To a solution of N-BOC-D-4-chlorophenyl-alanyl-N-(6-aminopyridin-3-yl)methyl-L-proline amide (1.30 g, 2.59 mmol) dissolved in ethyl acetate (10 mL), cooled to 0°C was bubbled in HCl (g) for 10 min. Reaction stirred an additional 0.5 h and was concentrated *in vacuo*. The residue was tritrated with ethyl acetate and filtered to provide 1.19 g of a white solid: mp 198-205°C. LRMS (M^+) 402.

Step F: Preparation of N-(t-butyloxy-carboxymethyl)-D-4-chlorophenyl-alanyl-N-(6-aminopyridin-3-yl)methyl-L-proline amide

To N-D-4-chlorophenyl-alanyl-N-(6-aminopyridin-3-yl)methyl-L-proline amide (0.80 g, 1.68 mmol) dissolved in 7 mL of DMF was added tert-butyl bromoacetate (0.30 mL, 1.84 mmol) and triethylamine (0.86 mL, 6.21 mmol). After 48 h the solution was diluted with 100 mL of ethyl acetate and washed with saturated $NaHCO_3$ (1x20 mL) water (4x20 mL), brine (1x20 mL), dried over $MgSO_4$

filtered and concentrated to a yellow oil. This was purified by flash column chromatography (30x150 mm column of SiO_2, CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH 60:39:1, 60:38:2, 60:37:3, 500 mL each) to provide a white solid. Recrystallization from ethyl acetate/hexanes afforded 0.232 g of a crystalline solid. mp 176-178°C. Anal. CHN:

	$C_{26}H_{38}N_5O_4Cl \cdot 0.1\ H_2O$
calc	C 60.30: H 6.66; N 13.53.
found	C 59.96: N 6.65, N 13.25.

EXAMPLE 12

Preparation of N-(N',N'diethyl-carboxymethyl)-D-4-chlorophenyl-alanyl-N-(6-amino-pyridin-3-yl)methyl-L-proline amide

As above in Example 12, Step F. replacement of tert-butyl bromoacetate with N, N-diethyl-2-bromoacetamide afforded the desired product. After flash column chromatography the product was isolated as a foam: TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 60:35:5) Rf = 0.36; ^1H NMR (400 MHz, $CDCl_3$), δ 1.01 (t, J = 1.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H); 1.60-1.65 (m, 1H), 1.69-1.83 (m, 2H), 2.00 (br s, 1H), 2.14-2.18 (m, 1H), 2.64-2.71 (m, 1H), 2.82 (d, J=7.5Hz, 2H), 3.09-3.18 (m, 3H), 3.25-3.33 (m, 4H), 3.34-3.49 (m, 3H), 4.27 (d, J=5.8Hz, 1H), 4.37 (br s, 1H), 4.52 (d, J=5.5Hz, 1H), 6.44 (d, J=8.5Hz, 1H), 7.12 (d, J =8.2Hz, 2H), 7.22=7.26 (m, 2H), 7.43 (dd, J=8.3 and 2.1Hz, 1H), 7.90 (d, J=14Hz, 1H), 8.14 (dd, J=10.8, 5.4Hz, 1H).

Anal. CHN: $C_{26}H_{35}N_6O_3Cl \cdot 0.35\ CH_2Cl_2$:

Calc	C 58.37: H 6.68; N 15.30
Found	C 58.73; H 6.87; N 14.93

EXAMPLE 13

Preparation of N-(2R)-azido-3-(3,4-methylenedioxyphenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl- L-proline amide

Step A: Preparation of 6-amino-3-cyano-2-methylpyridine

To a solution of 6-amino-3-bromo-2-methylpyridine (20.0g 0.1069 mol) in 40 mL of DMF was added copper(I) cynanide (11.50 g, 0.128 mol). The reaction mixture was refluxed under argon for 10 h. cooled to 80°C and poured into a solution of NaCN (21.50 g) dissolved in 70 mL water. This stirred for 1 h and was extracted with ethyl acetate (4 x 100 mL). The combined organic layer was washed with 10% NaCN (1 x 75 mL), water (1 x 75 mL) and brine (1 x 50 mL) and dried over $MgSO_4$. The solution was filtered, concentrated and the residue was tritrated with ethyl acetate and hexanes to provide the product as a tan solid (8.90 g): ^1H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 5.39 (br s, 2H), 6.35 (d, J = 8.55 Hz, 1H), 7.54 (d, J = 8.54 Hz, 1H).

Step B: Preparation of the dihydrochloride of 6-amino-3-(aminomethyl)-2-methylpyridine

To a solution of 6-amino-3-cyano-2-methylpyridine (10.38 g 78.04 mmol) in 300 mL of ethanol/ methanol (3:1) and 30 mL of 6N HCl was added 10% Pd/C (5.00 g). The solution was flushed with hydrogen and vigorously stirred. After 14 h the mixture was filtered through celite and washed with 500 mL of methanol. The volatiles were removed *in vacuo* to provide a yellow solid : ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 4.12 (s, 2H), 4.89 (s, 6H), 6.94 (d, J = 9.1 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H).

Step C: Preparation of (4R)-3-(3-(3,4-methylenedioxyphenyl)-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone

To a solution of 3-(3,4-methylenedioxyphenyl)propionic acid (10.93 g, 0.0563 mol) dissolved in THF was added triethylamine

(8.22 mL, 0.0589 mol) and cooled to -78°C. Trimethylacetylchloride (6.93 mL, 0.0563 mol) was added dropwise and the reaction was warmed to 0°C for 0.5 h and recooled to -78°C. To this was added a solution of (4R)-(3-phenylmethyl)-2-oxazolidinone (9.49 g, 0.0536 mol) and n-BuLi (22.5 mL, 2.5 M in hexanes, 0.563 mol) in 150 mL THF after stirring for 1 h at -78°C via cannula. After 1 h the reaction was warmed to 0°C and stirred an additional 2 h then quenched with 100 mL of 1/2 sat'd NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layer was washed with sat'd $NaHCO_3$ (1x100 mL), water (1x100 mL), and brine (1x100 mL), dried over $MgSO_4$, filtered and concentrated to an oil. Recrystallization from ethyl acetate and hexanes afforded 15.17 g (76% yield) of white crystalline product: mp 86-87°C.

Step D: Preparation of (3(2R),4R)-3-(2-azido-3-(3,4-methylene-dioxyphenyl)-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone

To a solution of N-(4R)-3-(3,4-methylenedioxyphenyl)-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (7.59 g, 21.5 mmol) dissolved in THF and cooled to -78°C was added KHMDS (46.0 mL, 0.5 M in toluene, 23.0 mmol) dropwise. After 1 h a precooled solution (-78°C) of trisyl azide (7.46 g, 24.15 mmol) dissolved in THF (50 mL) was added via cannula. The reaction was quench with glacial acetic acid (7.0 mL) after 3 minutes and stirred at RT for 6 h. Saturated NH_4Cl (50 mL) was added and the aqueous was extracted with ethyl acetate (2 x 75 mL). The combined organic layer was washed with sat'd $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The solid was recrystallized from ethyl acetate and hexanes to afford 5.74 g of a yellow white solid. mp 125-132; ^1H NMR (400 MHz, $CDCl_3$) δ 2.83 (dd, J=13.4 and 9.5Hz, 1H), 2.94 (dd, J=13.6 and 9.2Hz, 1H), 3.13 (dd, J=13.7 and 5.1Hz, 1H), 3.33 (dd, J=13.4 and 3.0Hz, 1H), 4.15-4.23 (m, 2H), 4.62-4.66 (m, 1H), 5.19 (dd, J=9.1 and 5.1Hz, 1H), 5.94 (s, 2H), 6.76-6.82 (m, 2H), 7.20-7.36 (m, 5H).

Step E: Preparation of N-(2R)-azido-3-(3.4-methylene-dioxyphenyl)-1-propanoic acid

To a solution of (3(2R).4R)-3-(2-azido-3-(3.4-methylene-dioxyphenyl)-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (5.743 g, 14.57 mmol) dissolved in 75 mL of dioxane cooled to 0°C was added a solution of LiOH (0.419 g, 17.49 mmol) dissolved in water (25 mL) and 30% H_2O_2 (8.27 mL). After 0.5 h ethyl acetate was added (15 mL) and the solution was concentrated to 25 mL *in vacuo*. The aqueous layer was acidified to pH 2 with 10% HCl and extracted with ethyl acetate (3x75 mL). the combined organic layer was washed with water (1x20 mL). brine (1x20 mL). dried over $MgSO_4$. filtered and concentrated to an oil. This material was used directly in the next step.

Step F: Preparation of N-(2R)-azido-3-(3.4-methylene-dioxyphenyl)alanyl-L-proline methyl ester

To a solution of (2R)-azido-3-(3,4-methylenedioxyphenyl)-1-propanoic acid (from above) dissolved in 30 mL of DMF was added L-proline methyl ester hydrochloride (2.53 g. 15.30 mmol). HOBt (2.06 g. 15.30 mmol). EDC (2.93 g. 15.30 mmol). cooled to 0°C and then added triethylamine (4.46 mL. 32.06 mmol). After 1 h the reaction was warmed to RT and stirred 18 h. then diluted with ethyl acetate (300 mL) and washed with sat'd $NaHCO_3$ (1x50 mL). water (3x50 mL). brine (1x50 mL). dried over $MgSO_4$. filtered and concentrated to an oil. The residue was purified by flash column chromatography (40 x 150 mm column of SiO_2. EtOAc:Hex gradient elution 1:2 1000 mL. to 1:1 500 mL) to afford 3.26 g of waxy solid. TLC (EtOAc:Hex. 1:2) R_f = 0.17; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78-1.82 (m. 1H), 1.97-2.40 (m. 2H), 3.02-3.15 (m. 3H), 3.64-3.74 (m. 4H), 3.84-3.89 (m. 1H), 4.40-4.52 (m. 1H), 5.92 and 5.93 rotamers (s, 2H), 6.68-6.75 (m. 3H).

Step G: Preparation of N-(2R)-azido-3-(3,4-methylene-dioxyphenyl)alanyl-L-proline carboxylic acid

To N-(2R)-azido-3-(3,4-methylenedioxyphenyl)alanyl-L-proline methyl ester (0.84 g, 2.43 mmol) dissolved in 6 mL of THF cooled to 0°C was added a solution of LiOH (0.62 g, 2.58 mmol) in 2 mL of water. After 0.5 h reaction was quenched by the addition of ethyl acetate (10 mL) and concentrated to a 3 mL volume. The solution was acidified to pH 2 with 10% HCl and extracted with ethyl acetate (3x 25mL). the organic layer was washed with water (1x10 mL). and brine (1 x 5 mL). dried over $MgSO_4$. filtered and concentrated to a white solid (0.748 g, 93% yield). ^1H NMR (400 MHz. $CDCl_3$) δ 1.81-1.98 (m. 3H). 2.25-2.28 (m. 1H). 2.96-3.19 (m. 3H). 3.55-3.62 (m. 2H).3.85 (dd. J = 8.1 and 6.9 Hz. 1H). 4.49 (dd. J = 7.9 and 2.9 Hz. 1H). 5.94 (s. 2H). 6.68-6.76 (m. 3H).

Step H: Preparation of N-(2R)-azido-3-(3,4-methylene-dioxyphenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl- L-proline amide

To a solution of (2R)-azido-3-(3,4-methylenedioxy-phenyl)alanyl-L-proline carboxylic acid (0.319 g, 0.961 mmol) dissolved in 4 mL of DMF was added 6-amino-3-(aminomethyl)-2-methylpyridine dihydrochloride (0.222 g, 1.05 mmol). EDC (0.202 g, 1.05 mmol), and HOBt (0.142 g, 1.05 mmol). cooled to 0°C and added the triethylamine (0.428 mL, 3.074 mmol). The reaction was warmed to RT after 1h and quenched after 16 h by diluting into 100 mL of ethyl acetate and washed with sat'd $NaHCO_3$ (1x25 mL). water (4x25 mL). brine (1x20 mL). dried over $MgSO_4$. filtered and concentrated to a foam. Flash column chromatography (25x150 mm column of SiO_2, CH_2Cl_2/CH_2Cl_2 saturated with NH_3/MeOH gradient elution 60:38:2 to 60:37:3) provided 0.324 g of an oil: TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 60:30:10) Rf = 0.34; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61-1.79 (m, 2H), 2.01-2.07 (m, 2H), 2.35 (s. 3H), 2.85-2.90 (m, 1H), 3.01 (dd, J=13.4 and 6.6Hz, 1H), 3.14 (dd, J=13.4 and 8.4Hz. 1H), 3.50 (t, J=2.7Hz. 1H). 3.83 (dd. J=8.4 and 6.6Hz. 1H), 4.20-4.31 (m. 2H), 4.42

(s, 2H), 4.53 (dd, J=7.8 and 1.8Hz, 1H), 5.93 (dd, J=2.0 and 1.3 Hz, 1H), 6.29 (d, J=8.2Hz, 1H), 6.65-6.74 (m, 4H), 7.27 (d, J=3.7Hz, 1H).

Step I: N-(2R)-amino-3-(3,4-methylenedioxyphenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl- L-proline amide

To N-(2R)-azido-3-(3,4-methylenedioxyphenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl- L-proline amide dissolved in 10 mL of ethanol and 2.99 mL of 10% HCl was added 10% Pd/C (0.30 g) and charged with hydrogen. After 2 h the reaction was flushed with argon and filtered through celite washing with absolute ethanol. The solution was concentrated *in vacuo* and the oil was tritrated with ethyl acetate to afford 0.21 g white solid. mp 178-188°C;

Analysis for • $C_{22}H_{27}N_5O_4$ • 2HCl 0.95 • H_2O

calc	C, 51.26; H, 6.04; N, 13.59
found	C, 51.22; H, 6.14; N, 13.28

EXAMPLE 14

Preparation of (2R)-N-(N-morphilino-2-acetamide)-3-(3,4-methylene-dioxyphenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl-L-prolineamide

To a solution of N-(2R)-amino-3-(3,4-methylenedioxy-phenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl-L-proline amide dihydrochloride (0.95 g, 0.184 mmol) in DMF (2 mL) cooled to 0°C was added N-morphilino-2-bromoacetamide (0.038 g, 0.184 mmol) and triethylamine (0.028 mL, 0.202 mmol). The reaction was warmed to RT over 3 h and after 19 h the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography (15 x 150 mm column of SiO_2, CH_2Cl_2/CH_2Cl_2 saturated with NH_3/MeOH gradient elution 60:39:1; 60:38:2; 60:37:3; 60:36:4) to provide 0.009 g of a white solid: TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 60:30:10) Rf = 0.15; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78-1.83 (m, 2H), 2.20-2.25 (m, 1H), 2.35 (s, 3H), 2.71 (dd, J=16.1 and 7.3Hz, 1H), 2.77 (d, J=7.3 Hz, 2H), 3.15 (d, J=14.5 Hz, 1H), 3.29 (d, J=14.5 Hz, 1H), 3.30-3.36 (m,

2H), 3.41-3.55 (m, 6H), 3.62-3.65 (m, 2H), 4.21-4.38 (m, 4H), 4.57 (dd, J=7.8 and 2.6Hz, 1H), 5.92 (dd, J=3.3 and 1.3Hz, 2H), 6.28 (d, J=8.2Hz, 1H), 6.62-6.73 (m, 4H), 7.26-7.28 (m, 2H).

EXAMPLE 15

Preparation of (2R)-N-(N',N'-diethyl-2-acetamide)-3-(3,4-methylene-dioxyphenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl-L-prolineamide

The titled compound was prepared Tin a manner similar to that described in Example 16 using N, N-diethyl-2-bromoacetamide in place of N-morphilino-2-bromoacetamide to afford an amphorous solid: mp 85-100°C; TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 60:30:10) Rf = 0.39;

Analysis for $C_{28}H_{38}N_6O_5 \cdot 0.45\ H_2O$

calc	C, 61.62; H, 7.00; N, 15.40
found	C, 61.65; H, 7.20; N, 15.12

EXAMPLE 16

(2R)-N-(N'-pyrrolidine-2-acetamide)-3-(3,4-methylenedioxy-phenyl)alanyl-N-(6-amino-2-methylpyridin-3-yl)methyl-L-prolineamide

This was prepared in a manor similar to that described in Example 16 using N-pyrrolidine-2-bromoacetamide in place of N-morphilino-2-bromoacetamide to afford an amphorous solid; mp 78-82°C; TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 60:30:10) Rf = 0.32;

Analysis for $C_{28}H_{36}N_6O_5 \cdot 0.50\ H_2O$

calc.	C, 61.64; H, 6.84; N, 15.40
found	C, 61.62; H, 6.77; N, 15.01

EXAMPLE 17

Preparation of N-BOC-D-3,3-diphenylalanyl-N-(6-amino-2-methyl-pyridin-3-yl)methyl-L-proline amide

To a solution of N-BOC-D-3,3-diphenylalanyl-L-Pro-OH (0.48 g, 1.096 mmol) in DMF (5 mL) cooled to 0°C was added EDC (0.23 g, 1.205 mmol), HOBt (0.162 g, 1.205 mmol), the dihydrochloride of 6-amino-3-(aminomethyl)-2-methylpyridine (0.253 g, 1.205 mmol) and then triethylamine (0.611 mL, 4.38 mmol). The reaction was warmed to RT after 1h and quenched after 16 h by diluting into 100 mL of ethyl acetate and washed with sat'd $NaHCO_3$ (1x25 mL), water (4x25 mL), brine (1x20 mL), dried over $MgSO_4$, filtered and concentrated to a foam. Flash column chromatography (25x150 mm column of SiO_2, CH_2Cl_2/CH_2Cl_2 saturated with NH_3/MeOH gradient elution 60:38:2 to 60:37:3) provided 0.525 g of a foam. The foam was dissolved in EtOAc (5 mL) and prepcipitated with hexanes (20 mL) to afford a white solid: TLC (CH_2Cl_2/CH_2Cl_2 saturated NH_3/MeOH, 65:30:5) Rf = 0.47; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.42-1.48 (m, 1H), 1.57 (m, 2H), 2.10-2.14 (m, 1H), 2.32- (s, 3H), 2.50-2.57 (m, 1H), 3.67 (dd, J=8.9 and 8.6Hz, 1H), 4.19-4.30 (m, 3H), 4.36 (dd, J=11.3 and 8.6Hz, 2H), 4.84-4.90 (m, 2H), 6.32 (d, J=8.24Hz, 1H), 7.16-7.41 (m, 13H).

CHN anal. for $C_{32}H_{39}N_5O_4 \cdot 0.45\ H_2O$.

Calc C, 67.93; H, 7.11; N, 12.38.

Found C, 67.92; H, 7.02; N, 12.42.

EXAMPLE 18

Preparation of N-D-3,3-diphenylalanyl-N-(6-amino-2-methylpyridin-3-yl)methyl-L-proline amide

To a solution of (0.452 g, 0.81 mmol) dissolved in ethyl acetate (10 mL), cooled to -78°C was bubbled in HCl (g) for 10 min. Reaction stirred an additional 4 h at 0°C and was concentrated *in vacuo*.

The residue was tritrated with ethyl acetate and filtered to provide 0.407 g of a white solid: mp 211-216°C,
CHN anal. for $C_{27}H_{31}N_5O_2 \cdot 0.70H_2O$ and 1.85 HCl
Calc. C, 60.32; H, 6.42; N, 13.03.
Found C, 60.32; H, 6.41; N, 12.78.

K_i for thrombin is the inhibition constant for the tested compound with human thrombin. K_i for trypsin is the inhibition constant for the tested compound with bovine trypsin. Rate constants were determined using the following *in vitro* procedures.

In vitro assay for determining proteinase inhibition

Assays of human a-thrombin and bovine trypsin were performed at 25°C in 0.05 M TRIS buffer pH 7.4, 0.15 M NaCl, 0.1% PEG. Trypsin assays also contained 1 mM $CaCl_2$.

In assays wherein rates of hydrolysis of a *p*-nitroanilide (pna) substrate were determined, a Thermomax 96-well plate reader was used was used to measure (at 405 nm) the time dependent appearance of *p*-nitroaniline. sar-PR-pna (sarcosine-Pro-Arg-p-nitroanilide) was used to assay human a-thrombin (K_m=125 μM) and bovine trypsin (K_m=125 μM). *p*-Nitroanilide substrate concentration was determined from measurements of absorbance at 342 nm using an extinction coefficient of 8270 $cm^{-1}M^{-1}$.

In certain studies with potent inhibitors (K_i < 10 nM) where the degree of inhibition of thrombin was high, a more sensitive activity assay was employed. In this assay the rate of thrombin catalyzed hydrolysis of the fluorogenic substrate Z-GPR-afc (Cbz-Gly-Pro-Arg-7-amino-4-trifluoromethyl coumarin) (K_m=27 μM) was determined from the increase in fluorescence at 500 nm (excitation at 400 nm) associated with production of 7-amino-4-trifluoromethyl coumarin. Concentrations of stock solutions of Z-GPR-afc were determined from measurements of absorbance at 380 nm of the 7-

amino-4-trifluoromethyl coumarin produced upon complete hydrolysis of an aliquot of the stock solution by thrombin.

Activity assays were performed by diluting a stock solution of substrate at least tenfold to a final concentration ≤ 0.1 K_m into a solution containing enzyme or enzyme equilibrated with inhibitor. Times required to achieve equilibration between enzyme and inhibitor were determined in control experiments. Initial velocities of product formation in the absence (V_o) or presence of inhibitor (V_i) were measured. Assuming competitive inhibition, and that unity is negligible compared $K_m/[S]$, $[I]/e$, and $[I]/e$ (where $[S]$, $[I]$, and e respectively represent the total concentrations, of substrate, inhibitor and enzyme), the equilibrium constant (K_i) for dissociation of the inhibitor from the enzyme can be obtained from the dependence of V_o/V_i on $[I]$ shown in equation 1.

$$V_o/V_i = 1 + [I]/K_i \qquad (1)$$

The activities shown by this assay indicate that the compounds of the invention are therapeutically useful for treating various conditions in patients suffering from unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, and reocclusion or restenosis of recanalized vessels.

Thrombin Inhibitors - Therapeutic Uses

Anticoagulant therapy is indicated for the treatment and prevention of a variety of thrombotic conditions, particularly coronary artery and cerebrovascular disease. Those experienced in this field are readily aware of the circumstances requiring anticoagulant therapy. The term "patient" used herein is taken to mean mammals such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

Thrombin inhibition is useful not only in the anticoagulant therapy of individuals having thrombotic conditions, but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, thrombin inhibitors can be added to or contacted with any medium containing or suspected of containing thrombin and in which it is desired that blood coagulation be inhibited, e.g. when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prothesis, cardiac prosthesis, and extracorporeal circulation systems

The thrombin inhibitors of the invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The thrombin inhibitors can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers manufactured by the Dow-Corning Corporation.

The thrombin inhibitors can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The thrombin inhibitors may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The thrombin inhibitors may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinlypyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the thrombin inhibitors may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The dosage regimen utilizing the thrombin inhibitors is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the thrombin inhibitors, when used for the indicated effects, will range between about 0.1 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 1.0-100 mg/kg/day and most preferably 1-20 mg/kg/day. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the thrombin inhibitors may be administered in divided doses of two, three, or four times daily. Furthermore, they can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will,

or course, be continuous rather than intermittent throughout the dosage regime.

For example, oral tablets can be prepared which contain an amount of active compound of between 100 and 500 mg, typically between 200 and 250 mg. Typically, a patient in need of thrombin inhibitor compound, depending on weight and metabolism of the patient, would be administered between about 100 and 1000 mg active compound per day. For a patient requiring 1000 mg per day, two tablets containing 250 mg of active compound can be administered in the morning and two tablets containing 250 mg of active compound can again be administered in the evening. For a patient requiring 500 mg per day, one tablet containing 250 mg of active compound can be administered in the morning and one tablet containing 250 mg of active compound can again be administered in the evening.

The thrombin inhibitors are typically administered as active ingredients in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the like, and consistent with convention pharmaceutical practices.

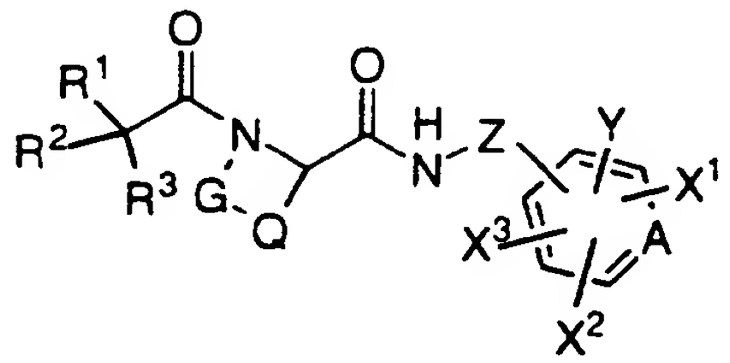
For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms

include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The thrombin inhibitors can also be co-administered with suitable anti-coagulation agents or thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various ascular pathologies. For example, thrombin inhibitors enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion. Thrombin inhibitors may be administered first following thrombus formation, and tissue plasminogen activator or other plasminogen activator is administered thereafter. They may also be combined with heparin, aspirin, or warfarin.

WHAT IS CLAIMED IS:

1. A compound having the following structure:



wherein

A is C or N;

X^1, X^2 and X^3, each independently attached to a ring carbon atom, are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

Y, attached to a ring carbon atom, is H, NH_2 or OH;

Z is $-(CH_2)_{1-3}-$;

R^1, R^2, and $R^{2'}$ are independently

hydrogen,

phenyl,

mono- or di-halogenated phenyl,

naphthyl,

biphenyl,

a 5- to 10-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,

C_{1-4} alkyl,

branched C_{1-4} alkyl,

C_{3-7} cycloalkyl,

C_{5-12} bicyclic alkyl,

C_{11-16} tricyclic alkyl,

$R^4(CH_2)_n$,

$(R^4)_2(CH)$,

$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is

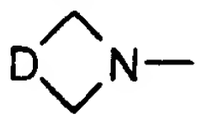
hydrogen,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 10-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
$-COR^5$,
$-OR^6$,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{1-4} alkoxy,

C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

R^5 is

-OH,
$-OR^6$,
$-N(R^7)_2$, where R7 is same or different, and



where D is $-CH_2CH_2-$, $-CH_2-O-CH_2-$, or $-CH_2-NH-CH_2-$;

R^6 is C_{1-4} alkyl;

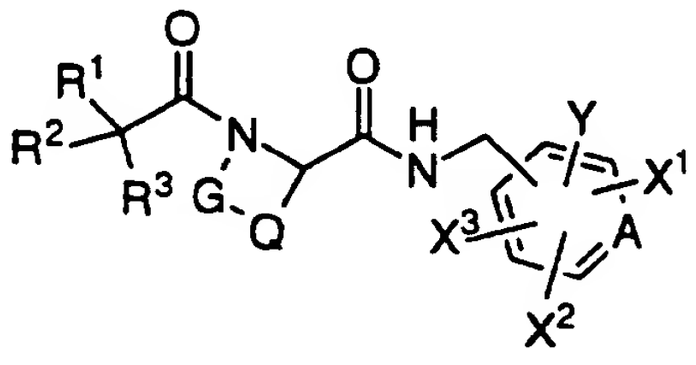
R^7 is hydrogen or C_{1-4} alkyl;

G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 having the following structure:



wherein
A is C or N;

X^1, X^2 and X^3, each independently attached to a ring carbon atom, are independently selected from the group consisting of
H and C_{1-4} alkyl;

Y, attached to a ring carbon atom, is H, NH_2 or OH;

R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2(CH)$,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S,

where n is 1, 2, 3 or 4;

R^3 is
H,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,

R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

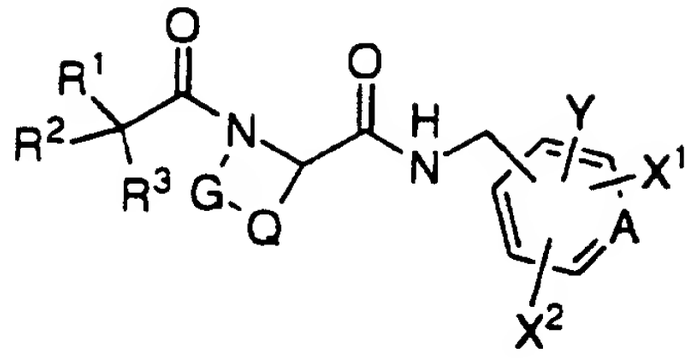
R^4 is independently
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 which has the structure:



wherein
A is C or N;
X^1 and X^2, each independently attached to a ring carbon atom, are independently selected from the group consisting of
H and C_{1-4} alkyl;
Y, attached to a ring carbon atom, is H or NH_2;
R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2(CH)$,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S,

where n is 1, 2, 3 or 4;

R^3 is

H,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently

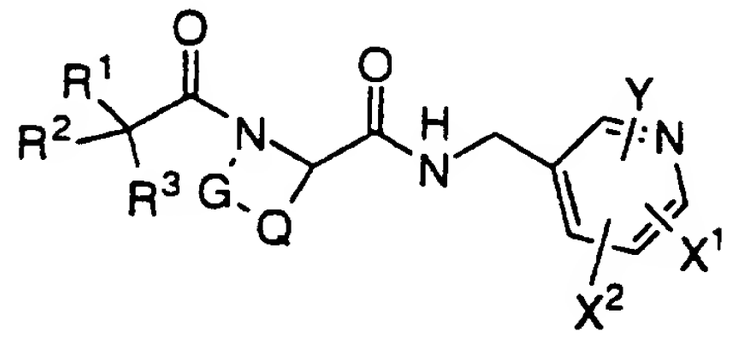
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2; or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

4. A compound of Claim 3 having the structure:



wherein

X^1 and X^2, each independently attached to a ring carbon atom, are independently selected from the group consisting of H and C_{1-4} alkyl;

Y, attached to a ring carbon atom, is H or NH_2;

R^1, R^2, and $R^{2'}$ are independently

hydrogen,

phenyl,

mono- or di-halogenated phenyl,

naphthyl,

biphenyl,

a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,

C_{1-4} alkyl,

branched C_{1-4} alkyl,

C_{3-7} cycloalkyl,

C_{5-12} bicyclic alkyl,

C_{11-16} tricyclic alkyl,

$R^4(CH_2)_n$,

$(R^4)_2CH$, wherein R^4 is the same or different,

$(R^4)(OR^4)CH$,

$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S,

where n is 1, 2, 3 or 4;

R^3 is
H,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

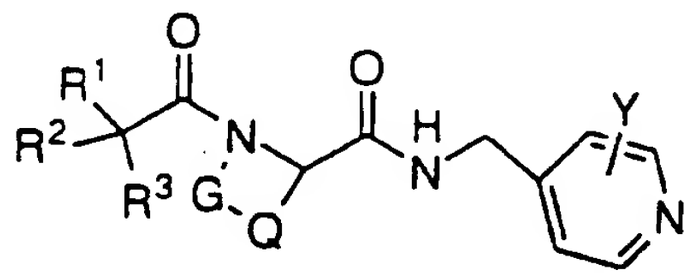
R^4 is independently
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2, or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

5. A compound of Claim 3 having the structure:



wherein

Y, attached to a ring carbon atom, is H or NH_2;

R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,
C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,

$R^4(CH_2)_n$,
$(R^4)_2CH$, wherein R^4 is the same or different,
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N, O and S.

where n is 1, 2, 3 or 4;

R^3 is

H,
$(R^2)_2N$, wherein R^2 is the same or different,
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen,
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently

phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
COOH,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,

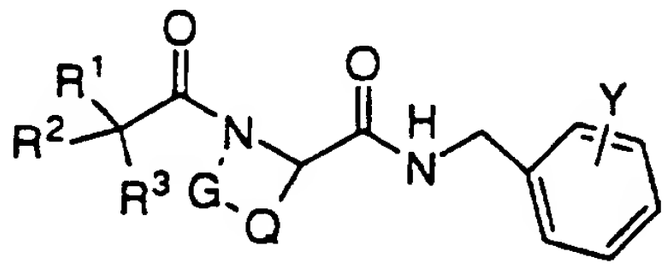
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

G is $(CH_2)_q$ where q is 1 or 2, or
NR^1CH_2; and

Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

and pharmaceutically acceptable salts thereof.

6. A compound of Claim 3 having the structure:



wherein

Y, attached to a ring carbon atom, is H or NH_2;

R^1, R^2, and $R^{2'}$ are independently
hydrogen,
phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to 7-membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S,
C_{1-4} alkyl,
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,

C_{5-12} bicyclic alkyl,
C_{11-16} tricyclic alkyl,
$R^4(CH_2)_n$,
$(R^4)_2CH$. wherein R^4 is the same or different.
$(R^4)(OR^4)CH$,
$R^4O(CH_2)_n$, or
R^1 may be joined with R^2 to form a four- to seven membered carbon ring in which zero to two carbon atoms may be substituted with heteroatoms independently selected from the list N. O and S.

where n is 1, 2, 3 or 4;

R^3 is

H.
$(R^2)_2N$, wherein R^2 is the same or different.
$R^{2'}OCONH$, provided $R^{2'}$ is not hydrogen.
R^2CONH,
$HO(CH_2)_p$, where p is 0, 1, 2, 3 or 4,
$R^{2'}SO_2NH$, provided $R^{2'}$ is not hydrogen, or
$(R^2)_mNCONH$, where m is 1 or 2, wherein R^2 is the same or different;

R^4 is independently

phenyl,
mono- or di-halogenated phenyl,
naphthyl,
biphenyl,
a 5- to-7- membered mono- or bicyclic heterocyclic ring or bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N. O and S,
COOH.
C_{1-4} alkyl.
branched C_{1-4} alkyl,
C_{3-7} cycloalkyl,

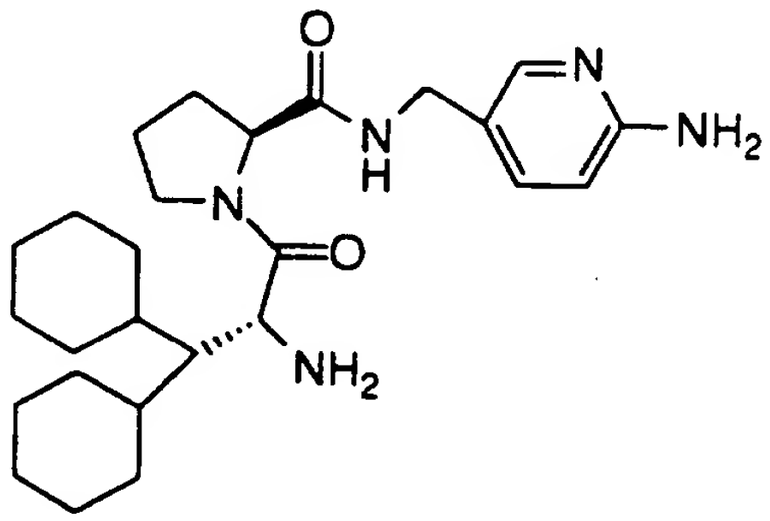
C_{5-12} bicyclic alkyl, or
C_{11-16} tricyclic alkyl;

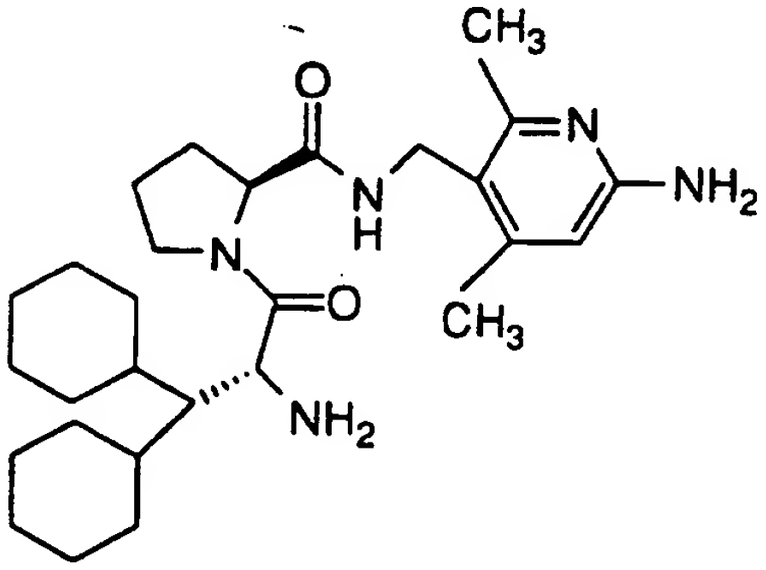
G is $(CH_2)_q$ where q is 1 or 2, or
NR^1CH_2; and

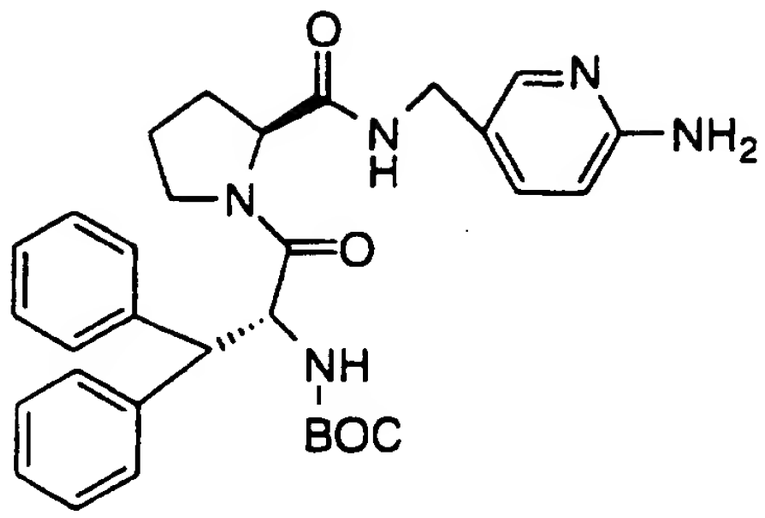
Q is SCH_2, or
$(CH_2)_r$ where r is 1 or 2,

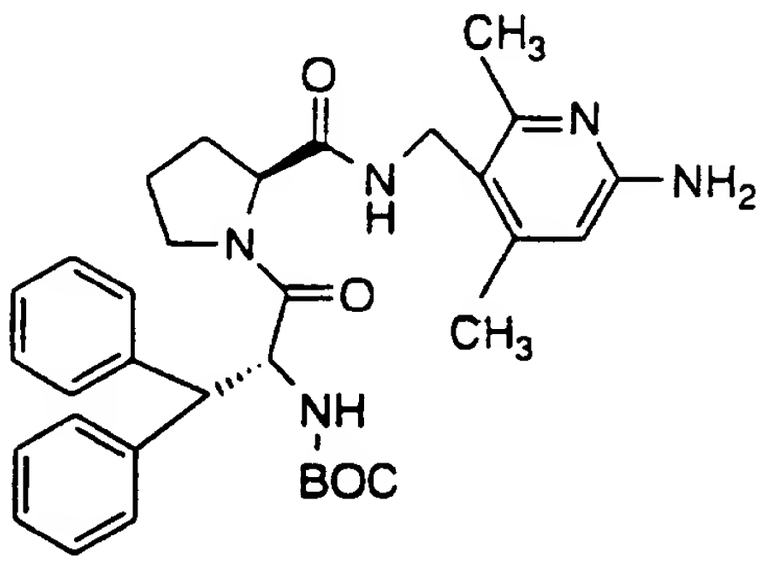
and pharmaceutically acceptable salts thereof.

7. A compound of Claim 3 selected from the group consisting of:

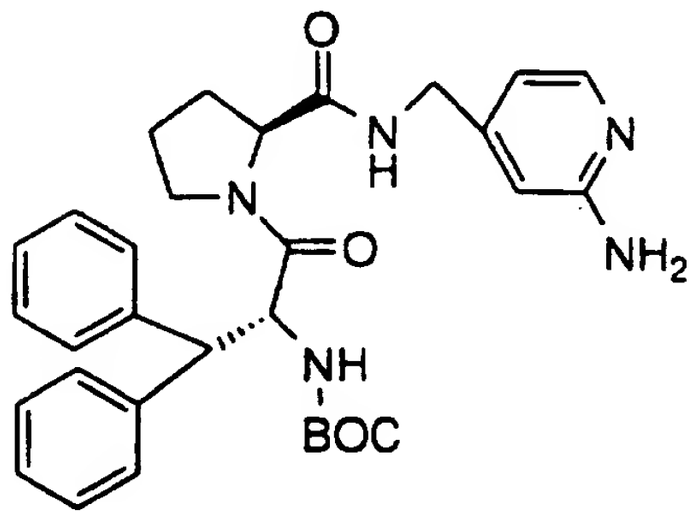








, and



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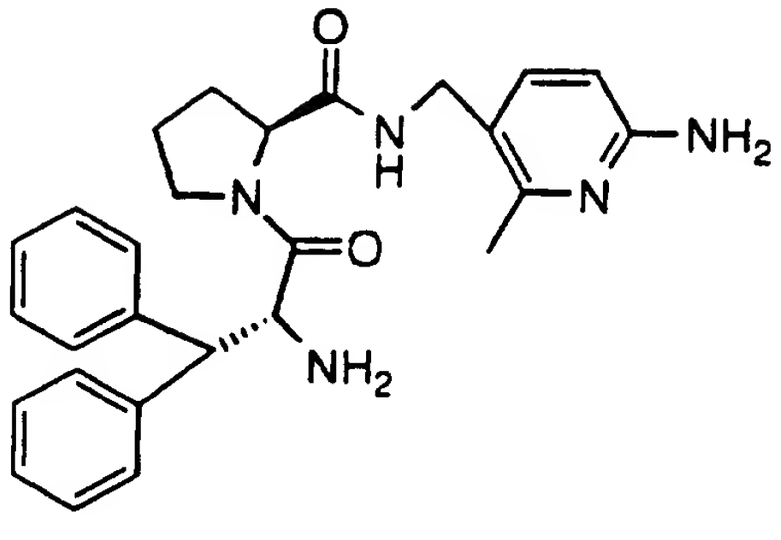

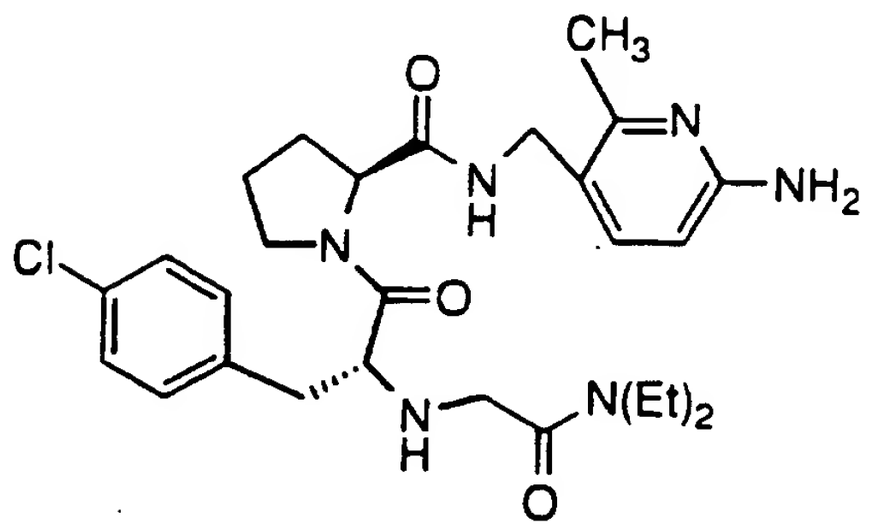

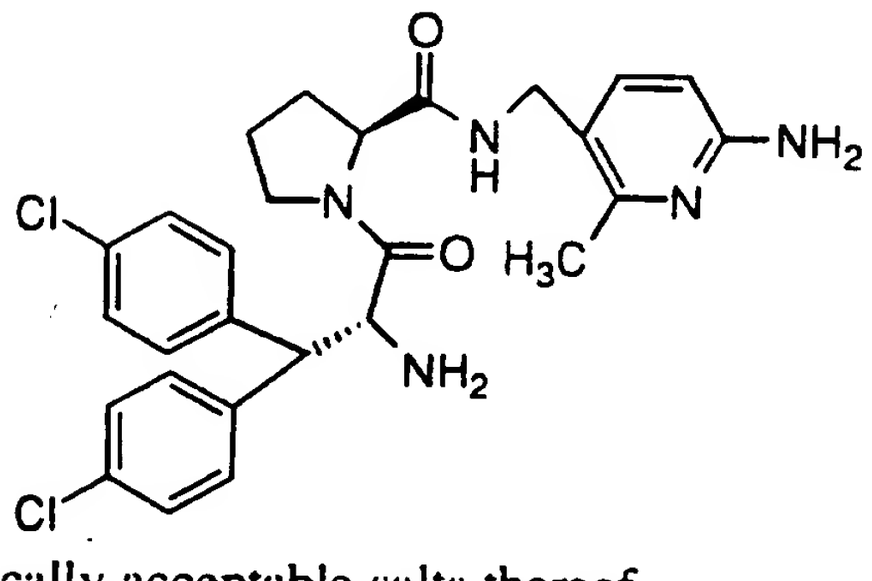

and pharmaceutically acceptable salts thereof.

8. A composition for inhibiting thrombin in blood comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

9. A composition for inhibiting formation of blood platelet aggregates in blood comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

10. A composition for inhibiting formation of fibrin in blood comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

11. A composition for inhibiting thrombus formation in blood comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

12. A method for inhibiting thrombin in blood in a mammal comprising administering to the mammal a composition of Claim 8.

13. A method for inhibiting formation of blood platelet aggregates in blood in a mammal comprising administering to the mammal a composition of Claim 9.

14. A method for inhibiting formation of fibrin in blood in a mammal comprising administering to the mammal a composition of Claim 10.

15. A method for inhibiting thrombus formation in blood in a mammal comprising administering to the mammal a composition of Claim 11.

16. A method for inhibiting thrombin in stored blood comprising administering to the mammal a composition of Claim 8.

17. A method for inhibiting formation of blood platelet aggregates in stored blood comprising administering to the mammal a composition of Claim 9.

18. A method for inhibiting formation of fibrin in stored blood comprising administering to the mammal a composition of Claim 10.

19. A method for inhibiting thrombus formation in stored blood comprising administering to the mammal a composition of Claim 11.

20. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting thrombus formation, preventing thrombus formation, inhibiting thrombin, inhibiting formation of fibrin, and inhibiting formation of blood platelet aggregates, in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/04460

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, E	US 5,510,369 A (LUMMA et al.) 23 April 1996, entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 10 JULY 1996	Date of mailing of the international search report 30 JUL 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE FAN Telephone No. (703) 308-4705

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/04460

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
7,and 1-6,8-20 (in part) GQ=(CH2)3,A=N no other hetero ring anywhere

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/04460

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

IPC(6) : C07D 401/12, 277/04, 205/04, 207/04, 279/00, 221/06, 285/16, 231/04 ; A61K 31/44, 31/445, 31/54, 31/40

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

U.S. 514/341,342,247,318,222.5,227.8,340,365,210,423,227.5,315,403; 546/279.1,269.7,268.1,194,275.4; 544/58.4,8,238; 548/200,953,538,356.1

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

U.S. 514/341,342,247,318,222.5,227.8,340,365,210,423,227.5,315,403; 546/279.1,269.7,268.1,194,275.4; 544/58.4,8,238; 548/200,953,538,356.1

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
Group I, claim 7, and the subject matter of claims 1-6,8-20 (in part) wherein GQ=-CH2-CH2-CH2-, A=N, no other hetero ring of any kind in all other variables.

Group II, claims 1-6,8-20(in part) wherein GQ=-CH2-CH2-, A=N, no other hetero ring of any kind in all other variables.

Group III, claims 1-6,8-20(in part) wherein GQ=-CH2-CH2-CH2-CH2-, A=N, no other hetero ring of any kind in all other variables.

Group IV, claims 1-6,8-20(in part) wherein GQ=-N-CH2-CH2-, A=N, no other hetero ring in other variables.

Group V, claims 1-6,8-20(in part) wherein GQ=-N-CH2-CH2-CH2-, A=N, no other hetero ring in other variables.

Group VI, claims 1-6,8-20(in part) wherein GQ=-N-CH2-S-CH2-, A=N, no other hetero ring in other variables.

Group VII, subject matter of group I but A=C.

Group VIII, subject matter of group II but A=C.Group IX,subjectof group III but A=C.

Group X, subject matter of group IV but A=C.

Group XI, subject matter of group V but A=C.

Group XII, subject matter of group VI but A=C.

Group XIII, the remaining subject matter containing different hetero ring in other variables.

The inventions listed as Groups I-XIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the compounds of above groups do not share a common core structure and are not so linked as to be obvious variants (equivalents) of each other and they are not interchangeable bioisosteres.